

Clinical Guidelines on **Allergy in Anaesthesia**

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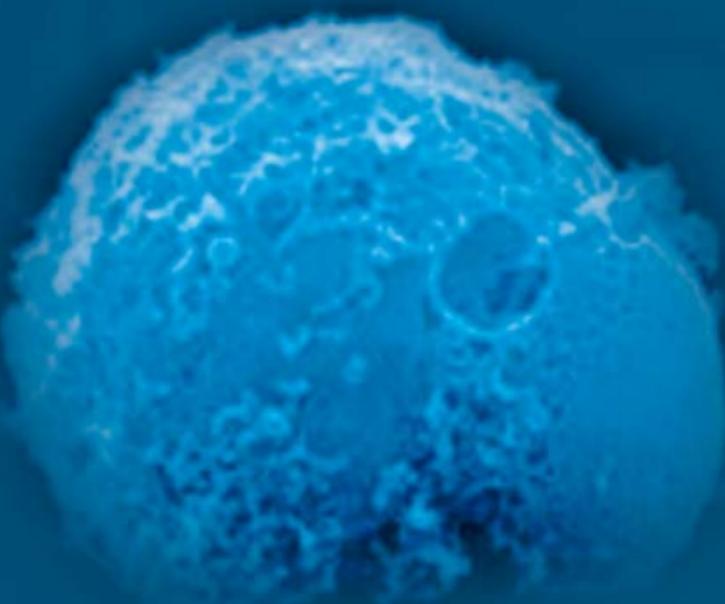
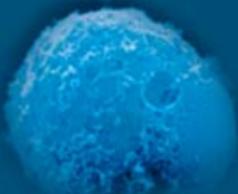
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Allergy in
Anaesthesia





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Biographies

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Professor of Anaesthetics, Queen's University, Belfast. Consultant Anaesthetist at The Royal Hospitals and the Belfast City Hospital Trust. He is a Member of the Council of the Royal College of Anaesthetists and past member of the Council of the Association of Anaesthetists of Great Britain and Ireland.

Professor Mirakhur's research interests cover neuromuscular block, intravenous anaesthesia and analgesia.



Dr Nigel J N Harper

Department of Anaesthesia,

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Consultant in Anaesthesia and Intensive Care at Manchester Royal Infirmary, UK, since 1984.

Dr Harper has a long-standing research interest in the clinical pharmacology of neuromuscular blocking drugs. Because neuromuscular blocking drugs are associated with a relatively high incidence of anaphylaxis, an interest in allergic responses during anaesthesia was a natural progression. In 1997 Dr Harper established an out-patient anaesthetic reaction clinic, run jointly with Dr Richard Pumphrey, Consultant Clinical Immunologist. Patients are referred from throughout the North-West of England. Dr Harper is also the chair of the Anaphylaxis Core Group of the Association of Anaesthetists of Great Britain and Ireland.

Dr Benoît Plaud

Adolphe de Rothschild Foundation, Paris, France

Head of the Anaesthesiology and Intensive Care Department at the Adolphe de Rothschild Foundation in Paris. Dr Plaud did his training in anaesthesiology and intensive care at the University of Paris. Besides clinical activities and teaching he has been involved for more than 10 years in research work on the pharmacology of neuromuscular blocking agents. Dr Plaud has been a visiting professor at the University of Montreal in the department of Professor François Donati.



Prof Rob C Aalberse

Sanquin Research and Diagnostics at CLB, Amsterdam, Netherlands

Prof Aalberse is a biochemist specialising in immunology, particularly IgE mediated allergy. Since 1969 Prof Aalberse has been working in allergy at the Dutch Central Blood Laboratory (CLB) where he has set up a well-known allergy department. Prof Aalberse is the Professor of Immunology at the University of Amsterdam and has some 200 peer-reviewed publications to his name.

1. Introduction

Although anaphylaxis is a rare event during anaesthesia, it can develop at great speed. It is therefore important that anaesthetists are aware of the symptoms and know what to do in the event of a suspected anaphylactic reaction. In addition, anaesthetists should know the importance of investigating such a reaction and how this is best performed.

The aim of this booklet is to provide the anaesthetist with a handy reference guide, providing practical guidance on the mechanism, diagnosis, treatment and possible prevention of anaphylaxis.

In addition, this booklet provides the anaesthetist with useful information on the tests that may be carried out to determine if a particular agent is the cause of an anaphylactic reaction.

In recent years there have been conflicting reports regarding the incidence of anaphylaxis with neuromuscular blocking agents (NMBAs). This booklet will therefore focus on the NMBAs in particular.

It should be remembered, however, that the science of allergy in anaesthesia still carries much uncertainty. There are important limitations to each step in the diagnosis of a suspected reaction, there is no gold standard test for anaphylaxis, and at least for today this is not yet an evidence-based science. This means that the interpretation of an event can be difficult, and even if an optimal procedure is followed there remains uncertainty about the exact cause of the event. This should be taken into account when reading this booklet.

2. Anaphylaxis

Anaphylaxis is a rapid, systemic hypersensitivity reaction to a substance in a sensitised individual with potentially life-threatening consequences. However, anaphylaxis is a rare event. Anaphylaxis is also known as a true allergic reaction.

Anaphylactic reactions can be due to a number of causes, as shown in Figure 1.

In the USA, it has been estimated that 1 to 17% of the population are at risk of anaphylaxis and of these 0.002% are at risk of the reaction being fatal. It should be noted that these figures relate to all causes, including food, drugs, latex and stings.¹

Although the exact incidence of anaphylaxis during general anaesthesia is unknown, estimates from epidemiological studies have reported a widely varying rate from 1 in 950 to 1 in 20,000 anaesthetics.²⁻⁵

It is generally believed that the incidence of drug induced anaphylaxis is increasing with the rise in the introduction of new drugs and as polypharmacy becomes the norm. It can be assumed that with the increasing awareness of and interest in allergy, more attention is given to it and therefore more reactions are reported. In many countries the reporting guidelines have been improved over the years and that has led to higher reporting rates.

The clinical manifestations of anaphylaxis can vary in onset, appearance and course. Common symptoms include cardiovascular effects (hypotension or cardiovascular collapse), the pulmonary

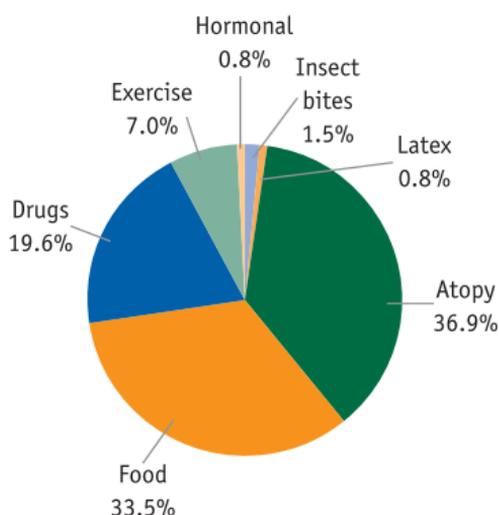


Figure 1. Some common causes of anaphylaxis¹

system in the form of bronchospasm, cutaneous signs (rash, erythema, urticaria) and angio- or generalised oedema. Many cases present with only one or two of these features.

Anaphylaxis can result in significant long-term morbidity, mainly related to cerebral hypoxia after an ineffective resuscitation. These reactions can be life threatening, in particular if adequate treatment is not started quickly.

Nomenclature

The traditional classification of anaphylactic/anaphylactoid reactions was:

- **Anaphylactic reaction:** immune (IgE positive) mediated reaction.
- **Anaphylactoid reaction:** non-immune mediated reaction.

This terminology was confusing and it was not always clear to anaesthetists and surgeons what the difference between the two was. It also posed a problem: how to refer to a reaction before it had been characterised by subsequent investigation.

In practice, it does not matter whether or not the reaction is IgE or non-IgE mediated. The immediate management of the patient is the same and the patient will need to avoid the drug in the future, irrespective of the mechanism of the reaction.

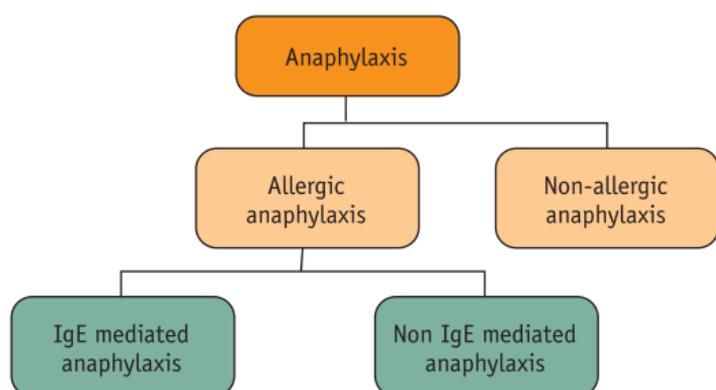
A task force set up by the European Association of Allergists and Clinical Immunologists to simplify how allergic reactions are described issued a revised nomenclature in 2001.⁶ The European task force recommended that anaphylaxis is now taken to mean both immune and non-immune mediated reactions. These reactions are subdivided into allergic anaphylaxis and non-allergic anaphylaxis. Allergic anaphylaxis may be IgE or non-IgE mediated. The new classification is shown in Figure 2. The task force has determined that the term ‘anaphylactoid’ should no longer be used.

When a patient experiences a suspected anaphylactic reaction, only subsequent investigations can establish whether the reaction was immune or non-immune in origin. However, these investigations may not result in a satisfactory answer for all cases. It is generally assumed that the effects of allergic anaphylaxis tend to be more severe, necessitating the early administration of epinephrine to restore cardiovascular and/or pulmonary function. In practice this is not

2. Anaphylaxis

Figure 2.

New classification of anaphylaxis⁶



always the case: non-allergic release of histamine and other mediators from mast cells can result in profound hypotension or bronchospasm.

The anaphylaxis described subsequently refers to allergic anaphylaxis unless otherwise specified.

Anaphylaxis during anaesthesia

True anaphylaxis during anaesthesia is very rare: many anaesthetists may never see such a reaction and few will see more than one during their working life.

However, because the consequences of anaphylaxis can be serious and potentially life-threatening, it is important for anaesthetists to know what the clinical signs are and how to deal with them.

The reported incidence of anaphylactic reactions during general anaesthesia varies considerably and has been estimated to be between 1 in 950 to 1 in 20,000 anaesthetic procedures.⁷⁻¹⁰ Accepted wisdom amongst anaesthetists is that the latter figure more accurately reflects the true situation in clinical practice. This large variation in reported incidence reflects the low risk involved.

Although rare, these reactions may be fatal, even when adequate treatment is given. The mortality rate is estimated to be between 3 and 6% of those who have an anaphylactic reaction.

3. Commonly used agents that cause anaphylaxis

It should be remembered that any agent, with the possible exception of the inhalational anaesthetic agents, could cause an allergic reaction. However, the reactions are more common with certain agents; these are listed in Table 1.

Table 1.
Commonly used agents causing anaphylactic reactions

Antibiotics
Aprotinin
IV anaesthetics, e.g. thiopental, propofol, midazolam
Latex rubber
Local anaesthetics
Neuromuscular blocking agents (NMBAs)
Non-opioid analgesics, e.g. NSAIDs
Opioid analgesics, e.g. morphine, alfentanil, fentanyl
Plasma volume expanders, e.g. gelatins, starches
Pre-medication drugs
Preservatives
Protamine
Radiocontrast media
Skin antiseptics, e.g. chlorhexidine, iodine

Figure 3 shows the causes of anaphylaxis as a percentage of the total number of cases in a 2-year study of anaphylaxis during anaesthesia conducted in France.²

Apart from this French study, there is little information regarding the incidence of anaphylaxis with different drug classes during surgery.

3. Commonly used agents that cause anaphylaxis

In the USA, penicillin, radiocontrast media, protamine and latex are the main causes of anaphylactic reactions related to medical intervention. NMBAs are not mentioned in this extensive review and do not appear to play an important role in anaphylaxis in the USA.¹

In comparison, a smaller Danish study showed that opioids, chlorhexidine and latex were responsible for more anaphylactic reactions than NMBAs (Figure 4).³ In this study, severe and mild reactions were investigated, all drugs and substances encountered before the reaction were tested and all patients were tested for latex and chlorhexidine. Tests carried out included measurements of mast cell tryptase, specific IgE and basophil histamine release, skin prick test, intradermal test and oral provocation and patch tests.

Although allergy to chlorhexidine and anaphylactic reactions to it are well described in the literature, it has been rarely tested for in France. Chlorhexidine is an important agent in the discussion of anaphylaxis during anaesthesia because it is widely used, particularly as a sterilising agent and as a coating for catheters. It may not be obvious to the staff that the patient has been in contact with chlorhexidine.

Although the comparative incidence may vary between different centres and countries, it is generally accepted that NMBAs are the most common cause of anaphylaxis during anaesthesia.

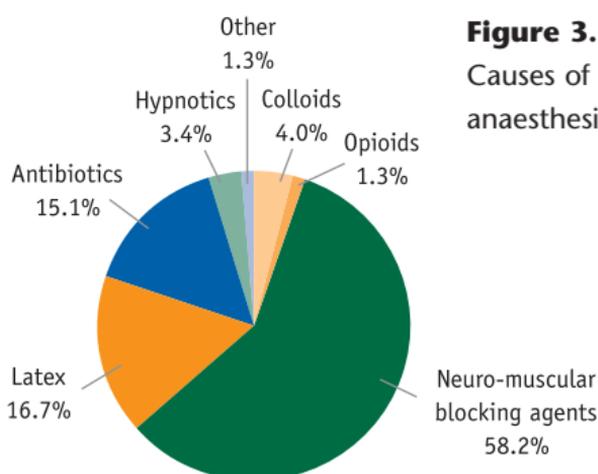


Figure 3.
Causes of anaphylaxis during anaesthesia in France²

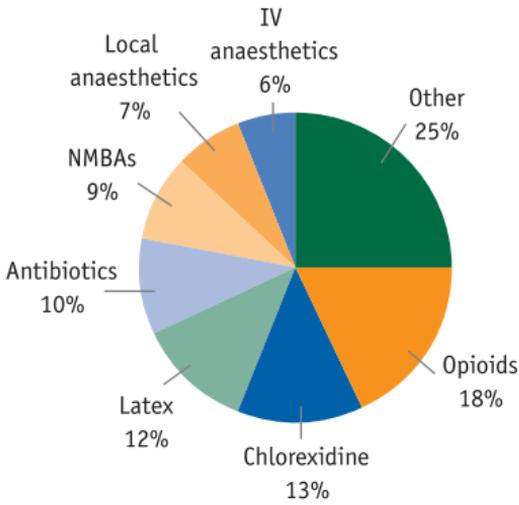


Figure 4.
Causes of anaphylaxis during anaesthesia³

Risk factors for anaphylaxis

Several factors are thought to affect the incidence of anaphylaxis—these are discussed below.

Atopy

Atopy is an important variable when antigen is administered via the skin or mucosal routes (e.g. orally) but not when it is administered parenterally.

Anaphylaxis is generally more common in atopic patients,¹¹ but opinion is divided concerning the relative importance of atopy in predisposing to succinylcholine anaphylaxis.^{12,13}

Route of administration

Anaphylaxis can occur with any route of antigen administration. However, it occurs more frequently and is often more severe when antigen is injected intravenously. In addition, the onset is more rapid after injection.

Age

Reactions are rare in children, probably due to a lack of previous exposure to allergens and lower susceptibility to the effects of the anaphylactic reaction. Reactions are thought to be more frequent in adults and the peak incidence appears to be in the fourth decade. Exceptions are children who have undergone many operations, such as those with spina bifida, who are considered at risk for latex allergy.

3. Commonly used agents that cause anaphylaxis

Previous anaesthetics

It has long been assumed that an increased number of general anaesthetics and therefore a more frequent exposure to the agents is also a factor for increased risk. However, no conclusive evidence for this has been found.

History of drug allergy

Another factor is a history of previous drug allergy. It has been observed that a reaction during a past anaesthetic was a risk factor for a reaction during subsequent anaesthetics. Any unexplained reaction during a previous anaesthetic might be an allergic reaction and should be considered a risk factor.¹⁴⁻¹⁶

Gender

Anaphylactic reactions to latex and NMBAs occur more frequently in women than in men (ratio 3:1).¹⁶ This difference may be due to exposure or a cross-reaction. For example, women are exposed to latex more frequently due to the preponderance of women working in healthcare, possibly accounting for a higher incidence of latex allergy in women. Females are also exposed more often to chemicals (e.g. those in cosmetics, soaps and detergents), which may lead to cross-sensitivity with other agents, including NMBAs. This does not imply that pre-anaesthesia testing is necessary or recommended for women.

NMBAs and reporting

Although NMBAs are possibly the most common cause of anaphylaxis during anaesthesia, anaphylaxis due to these agents is still a rare event with estimated rates differing significantly between countries and between reported studies.

The wide range in the reported incidence rates in different countries could be due to a number of factors, including:

- non-specific clinical presentation of anaphylaxis
- difficulty of correct identification of causative agent if several drugs were administered at the same time
- unreliability of testing methods and false positive and false negative results
- an increased level of publicity for a given drug or for a particular adverse drug reaction appears to influence reporting rates.¹⁷ Allergy

in general has received increased attention; however, particular (groups of) drugs have been focused on in certain countries

- lack of common testing and diagnostic methods
- intra- and inter-test variability
- variability in anaesthetic and surgical procedures employed
- varying use of individual NMBAs in different countries, making it difficult to estimate the number of patients exposed.

If rocuronium is taken as an example of a widely used NMBA, only a few anaphylactic reactions have been reported in the USA, although the majority of the exposure occurs there (estimated at more than 45 million patients). For atracurium, which is also used extensively, the number of anaphylactic reactions is similar to rocuronium in many countries according to the reported cases to the local authorities.

The evidence for a higher frequency of anaphylactic reactions with NMBAs than with other drugs is mostly based on case reports. Case reports are known to represent the lowest level of scientific evidence (Grade V).

While randomised controlled clinical trials should ideally be conducted to investigate the association between NMBAs and anaphylaxis, it is both unethical and impractical to do so considering there would be millions of patients required. Case-control studies could provide a better level of evidence but none have been conducted.

Other factors complicating the comparison of reported rates of anaphylaxis with individual NMBAs include the lack of agreed clinical criteria for an anaphylactic reaction and the fact that the tests for the different drugs have different:

- sensitivity – the proportion of individuals with the reaction who are correctly identified by the test
- specificity – the proportion of individuals without the reaction who are correctly identified by the test.

The incidence rate

The incidence rate is the number of anaphylactic reactions attributed to a particular drug per total patients who have undergone general anaesthesia with that drug. The resulting incidence is therefore dependent on both the numerator and the denominator of this equation.

3. Commonly used agents that cause anaphylaxis

To calculate the denominator it is necessary to estimate the total volume of drug used (usually derived from the sales in a particular country) and then estimating the average dose used per patient. This can vary from country to country and hospital to hospital since the habits, profiles and indications of drugs vary.

As the information on NMBA anaphylaxis comes from case reports, the reported incidence rates for individual NMBAs are affected by the varying levels of use and the tendency to report reactions in different countries. To illustrate this, consider two examples of varying levels of use. Some NMBAs are used more frequently in the Intensive Care Unit, where larger quantities are used for a single patient than in the operating theatre and usually for a prolonged period of time. While with succinylcholine in particular, there is a tendency to draw up the drug just in case it is required, and then discard the unused syringe at the end of the day. In both these examples, the total number of patients exposed to the drug is overestimated, affecting the incidence rate of anaphylaxis to that particular drug.

In terms of the numerator, it is impossible to know accurately how many reactions there have been to a particular drug.

There is no gold standard, so every description of a case is a matter of subjective probability. The clinical presentation of anaphylaxis is not always very specific, so it is often not clear whether a reported case is actually an anaphylactic reaction. In addition, the reporting of an anaphylactic reaction might be influenced by the clinician's perception that a particular drug might cause such a reaction.

For example, if propofol, fentanyl and succinylcholine were administered as the only drugs, the anaesthetist may suspect succinylcholine as the causative agent much more so than the other two drugs. In fact, since succinylcholine is known to cause anaphylaxis more commonly than propofol or fentanyl, it is possible that the patient would not be referred for testing and that the reaction would not be reported officially. Other examples are atracurium or mivacurium, drugs known to lead to non-specific histamine release. If a patient receiving these drugs presented with hypotension, skin erythema and increased airway pressure, all these symptoms would probably be considered as expected by the anaesthetist. Therefore the reaction, that could be a true allergic

reaction, would not be reported and/or investigated. One has to assume, however, that life-threatening reactions are reported nearly always to the authorities and/or the manufacturer, but the biases still affect these reports.

The reporting practice is also affected by the time a drug has been on the market. First reported by Weber of the Committee on the Safety of Medicines in the UK, and known as the Weber effect, newer drugs generate more reports than older drugs.¹⁸

In order to determine the true incidence of anaphylactic reactions with any agent and therefore to determine which drugs are involved most frequently, it is necessary to:

- have rigorous reporting
- know the denominator accurately (i.e. how many patients received the drug at that particular time)
- test all the agents to which the patient has been exposed and not just the ones suspected
- know the sensitivity and specificity of the tests performed. This is not possible since there is no gold standard available today. It is therefore important to understand that the results from testing will inherently include a degree of uncertainty
- have tests that are performed in the same way for all agents, so that even if the test may not be perfect, at least it is possible to compare the results from one agent with another.

Anaphylaxis to NMBAs from a global perspective

According to the Centers for Disease Control and Prevention (National Center for Health Statistics), in the USA for the year 2000 there were 23.2 million surgical procedures performed in hospital with all types of anaesthetic regime. This means that worldwide there are many tens of millions of procedures requiring general anaesthesia with an NMBA every year. It should be remembered that while anaphylaxis is a serious event that should not be taken lightly, it is also an event that is rare and does not feature as a prominent anaesthetic risk.

The incidence of anaphylactic reactions with individual NMBAs according to the French study is shown in Table 2.²

3. Commonly used agents that cause anaphylaxis

Table 2.

NMBAs involved in anaphylactic reactions during anaesthesia (n=306) ²		
NMBA	No. (%)	Market share in anaesthesia (vials), %
Rocuronium	132 (43.1)	8.8
Succinylcholine	69 (22.6)	6.7
Atracurium	58 (19.0)	54.1
Vecuronium	26 (8.5)	11.3
Pancuronium	10 (3.3)	9.5
Mivacurium	8 (2.6)	5.5
Cisatracurium	2 (0.6)	4.1

This was a retrospective review of 518 cases reported from 40 allergy centres in France of patients who had experienced an anaphylactic reaction during anaesthesia. The diagnosis was made on the basis of clinical history, skin tests and/or a specific IgE assay.

Of these cases, 306 (58%) were due to NMBAs and rocuronium was associated with the most reactions (132).

Because of the lack of specificity of the clinical signs, not all the patients diagnosed as having experienced an anaphylactic reaction may have done so. Several patients may have a diagnosis of anaphylaxis made solely on the basis of an IgE assay, some of which have not been properly validated. This is questionable, as good practice should involve a positive result to more than one type of test.

To demonstrate an association between anaphylaxis and the tests used, a case control study should be performed. A control group of patients is needed who were exposed to NMBAs but did not develop an anaphylactic reaction and who also underwent testing.

The incidence of anaphylaxis with NMBAs in France was estimated in a more recent study to be 1 in 15,000 or 1 in 312,000 if only the severe Grade IV reactions (4.9%) were taken into account. This was

based on the number of cases from the above study and an estimate of 5 million patients exposed to NMBA over the same time period from a survey of anaesthesia in France.¹⁹ This is a similar rate of incidence to that reported in other countries.

An increased incidence of anaphylaxis with NMBA was also reported in Norway.²⁰ Twenty-nine possible cases of anaphylaxis to rocuronium were reported and the exposure was estimated to be 150,000 patients, giving an incidence of approximately 1 in 5,000. However, patients were not specifically tested for rocuronium and other causes could not be excluded. It was concluded that problems related to small sample size, skewed distribution of data, statistical variance and different reporting priorities might explain the apparent high frequency of these anaphylactic reactions. Subsequently, the authorities published that after careful investigation, there was no evidence that rocuronium was any different from other NMBA in terms of allergy.²¹

The Danish Anaesthesia Allergy Centre issued preliminary results in 2001.³ Since 1999 this centre has been testing patients referred from all over the country and has devised a standard testing protocol. Testing includes all agents that were used during the anaesthesia, as well as antibiotics, colloids, latex and chlorhexidine. In the period reported, 36 patients had completed testing, and of these 21 patients tested positive. Only one patient was positive to a neuromuscular blocking agent whereas four patients tested positive for chlorhexidine.

In an Australian study it was shown that the rate of anaphylactic reactions with rocuronium in New South Wales was low, and that the increase in the number of reactions paralleled the increase in market share of this NMBA (Figure 5).²²

Comparing the relative propensity of each NMBA to cause positive intradermal tests in a population of known NMBA reactors, rocuronium is intermediate in its propensity to cause allergy together with atracurium and cisatracurium, compared with low-risk agents such as pancuronium and vecuronium, and higher-risk agents such as succinylcholine (Figure 6).²²

The USA is the largest NMBA market and no higher incidence of anaphylactic reactions to this group of drugs, or to one particular NMBA, is found. It has been stated that the reason for this large difference in incidence between France and the USA comes from differences in diagnosis.²³

3. Commonly used agents that cause anaphylaxis

Figure 5.
Anaphylaxis due to rocuronium and other NMBA²²

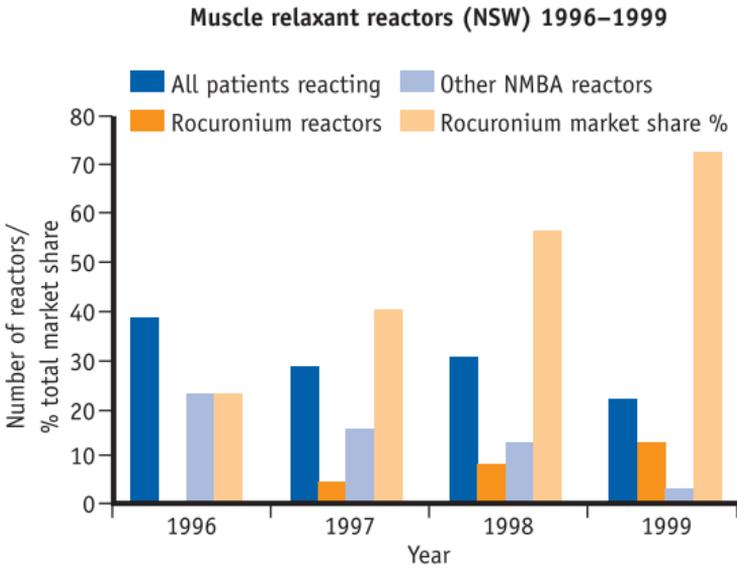
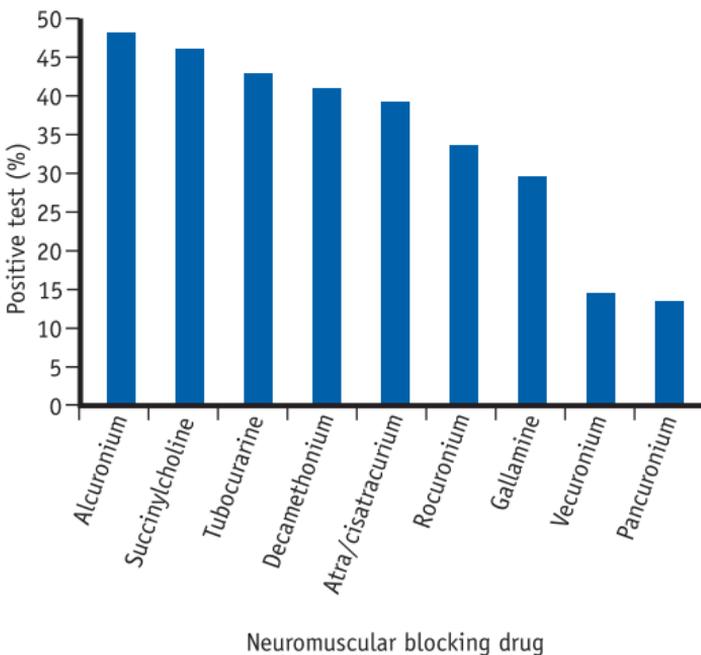


Figure 6.
Incidence of positive intradermal tests to NMBA²² in patients allergic to a NMBA²²



In summary, the only country reporting a higher incidence of anaphylactic reactions with rocuronium is France. In the UK there have been several case reports published about allergy with rocuronium,^{24,25} whereas there is no evidence of an increased incidence from the reporting system or from other sources.²⁶ In contrast, no evidence of an increased risk of anaphylaxis to rocuronium has been reported in Denmark, Finland, Sweden, Australia, the USA and Canada. Norway has investigated this topic and reached the same conclusion.

The importance of NMBAs in anaesthesia

Overall, NMBAs are associated with a low incidence of anaphylactic reactions. The older, depolarising NMBA succinylcholine is still widely used for its fast onset and short duration, particularly in patients with a full stomach who require rapid tracheal intubation.

The modern, non-depolarising NMBAs have become the preferred drugs in the majority of clinical situations and are the third pillar of general anaesthesia (together with analgesia and hypnotics). Their use in anaesthesia is important because they:

- facilitate and improve intubating conditions, therefore enabling the anaesthetist to secure the patient's airway quickly. NMBAs can also be life saving in emergency situations
- induce muscle relaxation, which is important for many types of surgery, such as those requiring access to the abdominal cavity
- induce complete immobility for microsurgery, delicate eye surgery, neurosurgery, thoracic surgery and a number of other intricate procedures.

Although there are risks associated with an anaphylactic reaction, particularly if not managed properly, the risk of pharyngeal/laryngeal trauma should not be underestimated in trying to avoid the use of NMBAs. Although it is possible to intubate the trachea without first giving a neuromuscular blocking drug, tracheal intubation without adequate muscle relaxation is associated with a relatively high incidence of laryngeal sequelae.

Although few studies have been conducted to assess the risk, the evidence indicates that the incidence of pharyngeal/laryngeal trauma is approximately 6% when a relaxant has not been given.²⁷⁻²⁹

3. Commonly used agents that cause anaphylaxis

In a study comparing tracheal intubation using propofol/fentanyl with and without atracurium, the addition of the NMBA significantly improved the quality of tracheal intubation and decreased postoperative hoarseness and vocal cord sequelae, which are a significant source of morbidity.³⁰ A recent study with propofol/alfentanyl induction with or without rocuronium showed that the muscle relaxant group scored better in terms of easier intubation, better hemodynamic conditions and less postintubation symptoms at 2 hrs and 24 hrs after extubation.³¹

4. Mechanisms of anaphylaxis

Definitions

- **Anaphylaxis** is a severe, life-threatening, generalised or systemic hypersensitivity reaction.
- **Hypersensitivity** causes objectively reproducible signs or symptoms, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects.
- **Hyper-reactivity** is an exaggerated normal response to a stimulus.

Mechanism of acute reaction

The most common mechanism for an anaphylactic reaction is the degranulation of mast cells and basophils with the subsequent release of inflammatory mediators, which are responsible for the symptoms and signs.

Anaphylaxis can result from either an immune (i.e. involvement of IgE) or a non-immune reaction. The generation of antibodies to a particular drug is largely unpredictable. It may be idiopathic or it may be related to environmental factors, and in several cases antibodies can be demonstrated while there has never been an exposure to the drug. These antibodies may have been induced by exposure to a different agent, such as bacterial phosphorylcholine, which may cross-react with NMBAs in the testing. The presence of these antibodies does not imply clinical reactivity.

In sensitised individuals, IgE antibody coats mast cells throughout the body. If a drug is administered during anaesthesia, which is reactive or cross-reactive with this IgE antibody, the mast cell becomes activated. This causes the immediate release of histamine, which peaks at approximately 5 minutes after the activation of the mast cells.

Histamine rapidly increases the permeability of blood vessels resulting in a loss of fluid from the intravascular to the extravascular space. A mild reaction is manifested as:

- flushing
- urticaria
- redness
- localised oedema.

In a more serious reaction, this is manifested as:

- shock (severe hypotension)

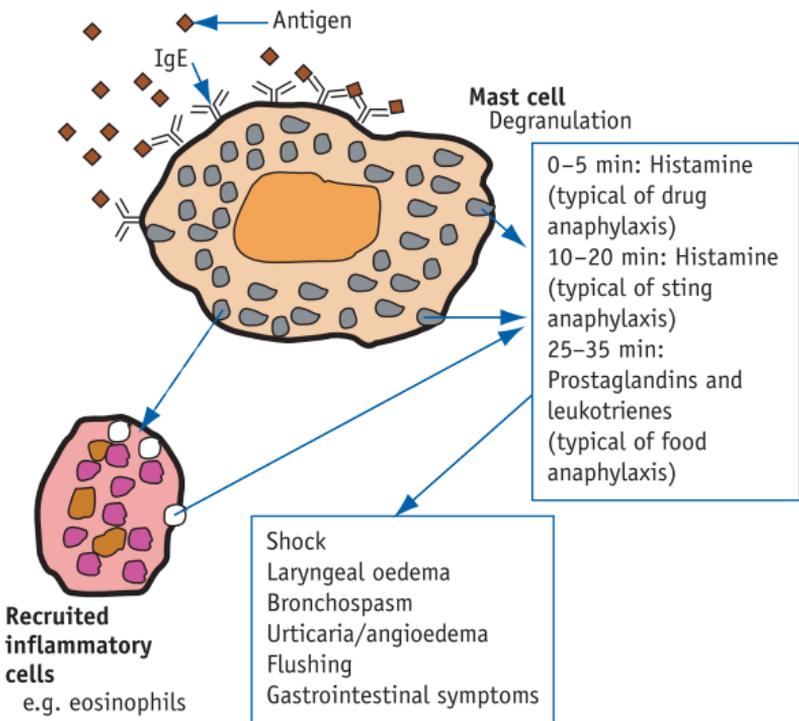
4. Mechanisms of anaphylaxis

- bronchospasm
- widespread oedema
- constriction of the airways leading to respiratory failure
- massive intravascular fluid loss resulting in dramatically reduced filling of the heart and subsequent severe hypotension.

The release of histamine also attracts other inflammatory cells, which in turn release more histamine. Approximately 20–35 minutes after the initial stimulus, mast cells start to secrete prostaglandins and leukotrienes, which can cause further redness and oedema.

Figure 7 shows the processes of antigen binding to IgE, the consequent degranulation of the mast cell and the results of histamine release. Trypsase is also released, as are other mediators including kinins, prostaglandins, leukotrienes and serotonin.

Figure 7.
Mast cell degranulation



The mechanisms of non-immunological mast cell activation are uncertain. They may involve degranulation to a varying degree, with the release of both histamine and tryptase, or the release of other inflammatory mediators, such as eicosanoids, without significant degranulation.

The mechanism of non-immunological release of mediators such as histamine is thought to involve membrane-associated enzymes, e.g. phospholipase A2 and phospholipase C, which are involved in arachidonic acid synthesis and metabolism.

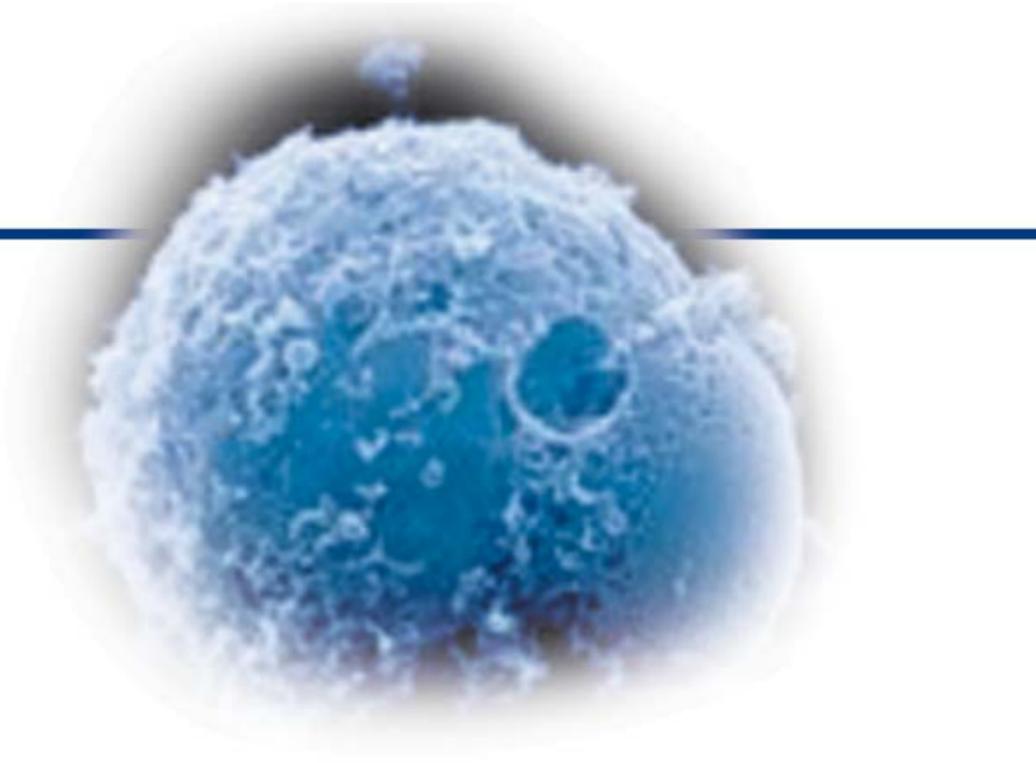
NMBAs

All NMBAs contain at least one quaternary ammonium group by which they combine with the post-synaptic nicotinic receptor to exert their pharmacological effect.

For NMBAs, the main antigenic determinant is the quaternary ammonium ion capable of bridging the IgE antibodies and triggering anaphylaxis. The flexibility of the chain between the ammonium ions as well as the distance between them may be of importance, where flexible molecules such as succinylcholine are able to bridge more easily than rigid molecules such as rocuronium and vecuronium. This would explain why succinylcholine appears to be more allergenic than the non-depolarising NMBAs.

Quaternary ammonium groups are ubiquitous in consumer products or in other means of exposure, e.g.

- perfumes
- soaps
- polishes
- sprays
- foodstuffs
- bacteria (many contain phosphorylcholine on their cell wall which is known to cross-react with NMBAs).



5. Diagnosis of anaphylaxis

When signs and symptoms appear after several drugs are administered sequentially, as occurs during induction of anaesthesia, it does not mean that the drug administered last is the cause.

Clinical symptoms

The clinical symptoms of anaphylaxis are shown in Table 3.

Table 3.
Clinical symptoms of anaphylaxis²

Symptom	Frequency
Cardiovascular symptoms	74.7%
Cutaneous symptoms	71.9%
Cardiovascular collapse	50.8%
Bronchospasm	39.8%
Hypotension	17.3%
Angioedema	12.3%
Cardiac arrest	5.9%
Bradycardia	1.3%

The clinical features of anaphylaxis vary widely from patient to patient, from mild to severe shock. Anaphylaxis may occur at any time during anaesthesia and progress slowly or rapidly. In most cases, the faster the onset of symptoms, the more severe the reaction.

The clinical symptoms and signs of anaphylaxis usually begin to appear within 5 to 30 minutes after antigen injection but can occur within seconds. If signs appear later during the maintenance of anaesthesia, they suggest allergy to latex or volume expanders.

In serious cases, initially the respiratory and cardiovascular systems are often affected. It is important to note that hypotension is the only presenting sign in about 10% of cases of allergic anaphylaxis.

5. Diagnosis of anaphylaxis

One of the commonest early signs of anaesthetic anaphylaxis is difficulty in inflating the lungs prior to tracheal intubation.

Severe upper airway obstruction caused by angioedema can lead to asphyxia. Lower airway obstruction caused by bronchospasm results in wheezing and chest tightness.

Severe hypotension is caused by a massive shift of fluid from the intravascular to the extravascular space as a result of increased vascular permeability. Cardiac filling is reduced dramatically and hypotension ensues. The loss of intravascular volume can be rapid and profound: up to 50% can be lost within 10 minutes.

Gastrointestinal symptoms include nausea, vomiting, diarrhoea and abdominal pain. Cutaneous signs include flushing, urticaria and angioedema.

Cardiac symptoms are varied and can be profound. Characteristically, a compensatory tachycardia occurs in response to the decreased effective vascular volume or vasodilatation. Bradycardia, resulting from an increase in vagal tone, can also occur.

Table 4 shows the classification of anaphylaxis according to clinical severity. The figures for hypotension refer to an absolute fall in systolic arterial pressure.

Table 4.
Classification of anaphylaxis according to clinical severity

	Grade	Skin	Respiratory	Cardiovascular
Mild	I	Flush	–	–
	II	Urticaria Flush	Increased pulmonary resistance	Marked tachycardia Hypotension (SAP –20mm Hg)
Life-threatening	III	Urticaria Flush	Bronchospasm Cyanosis	Major hypotension (SAP –60mm Hg) Shock
	IV	Urticaria Flush	Respiratory arrest	Shock Cardiac arrest

Differential diagnosis

When a patient presents with sudden symptoms of pulmonary resistance, flushing or hypotension, rapid assessment is essential so that appropriate treatment can be given.

A number of conditions other than anaphylaxis can cause similar symptoms and need to be considered in the differential diagnosis.

Other forms of shock, including cardiogenic, haemorrhagic and endotoxic, must be considered. However, it is usually easy to distinguish between these and anaphylaxis.

Flushing syndromes often mimic anaphylaxis. These include carcinoid syndrome (rare), postmenopausal flush, idiopathic flush and flush due to medullary carcinoma of the thyroid (rare). It should also be remembered that some drugs are histamine releasers, e.g. opioids and some NMBA, which can produce flushing without this being an allergic reaction.

Testing is an important part of the diagnosis of anaphylaxis. The next chapter gives further details about these investigations.

Rule out other causes

It is important to remember that not every serious reaction is anaphylaxis. In diagnosing the clinical symptoms and signs of allergy, a number of causes need to be excluded first such as:

- exaggerated hypotensive response to the induction agent in the presence of chronic antihypertensive medication, hypovolaemia or covert pre-existing cardiac impairment;
- bronchospasm resulting from the mechanical effects of endotracheal intubation in susceptible patients;
- vagal response causing severe bradycardia (e.g. during laparoscopy, ophthalmic procedures, etc);
- covert haemorrhage;
- unexpectedly extensive sympathetic blockade during extradural or intrathecal neuraxial anaesthesia;
- acute exacerbation of pre-existent asthma independent of anaesthesia;

5. Diagnosis of anaphylaxis

- covert airways obstruction, breathing system malfunction, undetected oesophageal intubation;
- pulmonary aspiration of gastric contents;
- embolism (thrombotic, fat, air, amniotic fluid, tumour, etc);
- acute myocardial infarction;
- malignant hyperpyrexia;
- drug administration error.

6. Testing

In many countries there is a general lack of testing procedures. In countries where testing does take place, there are usually no accepted standard protocols; thus the methods used vary both within and between countries. As a consequence, the results obtained are highly variable and it is difficult to compare findings in different centres and different countries. Moreover, certain tests are available in some countries and not others.

It is important to understand that any one test alone does not provide a clear picture of what has happened. There is no gold standard. Therefore, a number of different tests must be performed in order to make a more accurate diagnosis and determine the agent or agents most likely to cause the anaphylactic reaction.

Testing is of value for the individual patient, to determine the most likely drug involved and therefore to avoid that drug in the future. However, a positive test result does not prove that the patient is allergic to the drug, or that the symptoms seen were due to allergy to that drug, as false positive reactions can occur.

Immediate investigation of samples collected before, during or after the event centres around blood testing and is focused on identifying whether a reaction is likely to have been of an immunological nature. Delayed investigation involves skin testing and is focused on identifying the likely causative agent.

Blood testing

Blood testing for mediators is useful in identifying the reaction type but does not isolate the cause where multiple drugs have been administered.

Histamine

An increase in plasma histamine can be related to anaphylaxis or a non-specific reaction. A blood sample should be taken as soon as possible after the reaction:

- Grade I: 5–15 minutes
- Grade II: <30 minutes
- Grade III/IV: 10–120 minutes.

The criteria for storing and processing blood samples for histamine assay are so rigorous as to make this test impractical to use and it is therefore not recommended.

6. Testing

Urinary methylhistamine assays are no longer commonly used due to their low sensitivity in comparison with other tests.

Mast cell tryptase

Tryptase is released by degranulating mast cells. The normal value is <13ng/mL. An elevated mast cell tryptase level indicates mast cell activation but is not specific for anaphylaxis. Tryptase can also be performed on post-mortem samples. False positive results for anaphylaxis have been reported, involving cases of extreme stress, such as hypoxia or severe trauma.^{32,33}

Serum tryptase has a half-life of 90 minutes and reaches a peak 15–120 minutes after the reaction.

Blood samples should be taken:

- as soon as the situation is under control
- 1–2 hours later.

The blood sample required for the tryptase determination is collected in an EDTA tube and the plasma separated. A serum sample from clotted whole blood is also possible. Samples may be frozen prior to analysis and prior to transport to a specialist laboratory.

Without a tryptase result (currently approximately 50% of cases), the diagnosis is much less certain.

IgE antibody

IgE antibody testing should be performed and has even been proved to be useful years later or even post-mortem. It has been stated that testing should be employed 4 to 6 weeks after the event. However, it can be argued that it should be performed much sooner at 2 to 3 days after the event or on blood drawn at the time of the reaction if it is available. This earlier timing would detect antibodies that were present during the reaction and remove the possibility of testing for new antibodies that were not present during the reaction but were formed after.⁵

Unfortunately, very few assays are commercially available to test for IgE specific to anaesthetic drugs (see below) and this factor limits the usefulness of these tests in practice. A few specialist centres have developed their own specific IgE tests. The only neuromuscular blocking agent for which a specific IgE test is commercially available is succinylcholine. However, specific IgE testing is an integral part of the investigation of possible latex allergy.

Total IgE levels vary in the normal population: as much as from 0 kIU/L to >2,500 kIU/L. At present, specific IgE tests are not corrected for total IgE levels. However, correction is important as a very high total IgE (>2000 kIU/L) may result in a false-positive IgE antibody test.

Specific IgE can be measured by fluoroimmunoassay (CAP system, Pharmacia) or radioallergosorbent test (RAST). However, specific IgE tests are only readily available for a small number of substances (see Table 5). It will be necessary to check with the laboratory their exact requirements for blood samples and whether these may be frozen prior to transport.

Table 5.
CAP (Pharmacia) tests for specific IgE

Amoxycilloyl
Ampicilloyl
Penicilloyl G
Gelatin
Insulins, chymopapain, ethylene oxide
Latex
Penicilloyl V
Protamine
Succinylcholine

The result of the IgE antibody test will be negative or positive, indicating that specific antibodies to the test substance were or were not found in the serum. Although a positive IgE antibody test is not proof that an anaphylactic reaction has occurred, IgE antibody testing is more informative than tryptase measurements. The results of the IgE antibody testing, tryptase and skin tests should be used together to determine the likely cause of the reaction.

6. Testing

Skin testing

A trained immunologist or allergist must perform skin tests, preferably at a centre with experience of anaesthetic testing.

Before skin tests are performed, it is important that clinical information is provided to the immunologist performing the test:

- the type of anaesthesia and surgery performed
- a list of all the drugs used prior to and during the procedure including skin disinfectants
- the timing of clinical events regarding drug administration
- degree of cardiovascular depression/collapse
- the results of any blood tests that have already been performed, such as histamine or tryptase
- a copy of the patient's allergy history.

Skin testing is usually performed 6 weeks after the reaction. Theoretically, it would be better to test earlier but practically this is not possible since the patient will have received therapy for the reaction and is most likely using antihistamines.

Patients should discontinue their antihistamine medication for at least 24 hours prior to testing, as this will influence the results. Many drugs have antihistamine properties, including some anti-depressants, cough suppressants and herbal remedies. Many commonly available analgesics contain codeine and these should be discontinued before testing.

Skin testing is usually performed on the anterior face of the forearm. In France, however, testing is mainly carried out on the back.

It is important to test all drugs administered to the patient during the perioperative period, including intravenous colloids, and the agents with which the patient may have come into contact, such as latex and chlorhexidine, regardless of which drug is suspected. If an NMBA was part of the drugs administered, then it is important to test for all NMBAs because of the high incidence of cross-sensitivity, which is as high as 70%.¹⁶ This means that a patient who is reactive to one NMBA has a greater chance of also being reactive to other NMBAs. It could be speculated that these patients would have had a reaction regardless of which NMBA was chosen for the anaesthesia.

Skin responses are compared with a positive (codeine phosphate or histamine) and a negative (saline) control. This is important, as approximately 5% of patients will show a positive response to saline.

Freshly prepared and diluted drugs should be used. Some centres use drug dilutions made up in phenolic saline solution and stored in a refrigerator for repeated use. However, the chemical stability of NMBAs in this diluent, at the concentrations used for skin testing, has not been determined. Degradation of the test drug may occur in dilute solution over time and the test solution will contain a mixture of the parent drug, degradation products and phenol.

External factors that can affect the results of skin tests are shown in Table 6.

Table 6.
Skin tests: confounding factors

Suppress response	Antihistamines H2 blockers Antidepressants Cough medicines Topical steroids
Enhance response	β blockers NSAIDs Opioids (including codeine)

There are a number of important questions with skin testing. These are shown in Table 7.

Table 7.
Questions about skin testing

1	Is the reaction IgE mediated?
2	How can the results be interpreted for drugs with intrinsic histamine-releasing activity? e.g. atracurium, mivacurium, opioids
3	What is the optimal concentration for testing?
4	What wheal size is significant? And at what concentration?
5	Should the flare be taken into account?

6. Testing

Concentrations used for skin testing

It has been questioned whether the correct diagnosis is being made and the issues surrounding allergy testing and the need for standardisation have been highlighted.²³

Drug test doses are selected on the basis of the concentration that is least likely to initiate a non-specific wheal and flare response (i.e. a false positive result). This means that the concentration that is tested should be just right: not too concentrated (as few false-positive results as possible) and not too dilute (as few false-negative results as possible). The determination of the concentration for individual drugs is mainly based on the observation of sequential concentration increases in reactive individuals.

Drugs that directly release histamine from mast cells can give false positive responses. These include atracurium and morphine. For these drugs, lower concentrations should be used in an attempt to prevent false positives. However, lower concentrations increase the risk of false negative reactions and therefore the testing of these drugs is less accurate than for other non-histamine releasing drugs tested at a higher concentration.

NMBAs are highly charged molecules that have the ability to produce a positive wheal and flare response independent of IgE antibodies. In addition, steroid-derived NMBAs have direct vasodilating properties. These effects can lead to a false positive response that can confuse skin testing and interpretation. Evidence is now emerging that at certain concentrations NMBAs elicit false positive skin reactions in volunteers. From Norway, France and the USA there is now evidence that rocuronium and cisatracurium can cause false positives at dilutions used for skin testing.³⁴⁻³⁶

The appropriate threshold concentration for skin testing of each drug must be determined. This can be done, for example, by investigating the effects of intradermal injections of increasing drug concentrations on wheal and flare responses in naïve volunteers. Ideally, the repeatability and reproducibility of skin tests should be evaluated and the accuracy of skin tests assessed in volunteers. It should be remembered that there is inter-individual variability in sensitivity.

Table 8 gives more detail about the recommended concentrations for various drugs. There is considerable controversy about the optimal concentration to be used as there are only few studies that have studied this in assessor-blind clinical trials with naïve volunteers. It is important to note that when these concentrations are looked at in Molar units, it becomes apparent that there are large differences in the number of molecules injected into the skin for the various NMBAs. This makes a comparison between the drugs questionable.

Table 8.
Recommended testing concentrations

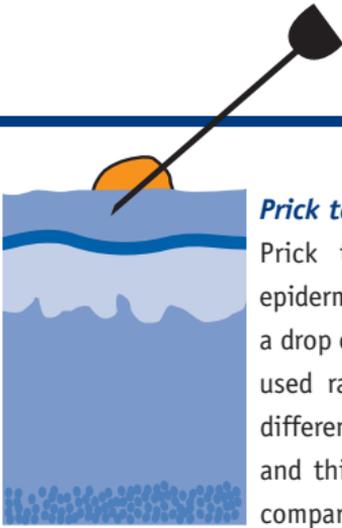
	Concentration supplied by manufacturer	Prick testing dilution used for testing, also in Molar for NMBAs	Intradermal dilution used for testing, also in Molar for NMBAs	Relative number of NMBA molecules injected intradermally if Mivacurium is set at 1
Succinylcholine chloride <i>Molecular weight= 397.3 g/mole</i>	50 mg/mL 1.26×10^{-1} M	1:5 2.5×10^{-2} M	1:500 2.5×10^{-4} M	150
	10 mg/mL 2.5×10^{-2} M	Undiluted 2.5×10^{-2} M	1:100 2.5×10^{-4} M	150
Atracurium besylate <i>Molecular weight= 1243.4 g/mole</i>	10 mg/mL	1:10	1:1000	5
	8×10^{-3} M	8×10^{-4} M	8×10^{-6} M	
Cisatracurium besylate <i>Molecular weight= 1243.4 g/mole</i>	2 mg/mL	Undiluted	1:100	10
	1.6×10^{-3} M	1.6×10^{-3} M	1.6×10^{-5} M	
Mivacurium chloride <i>Molecular weight= 1100.18 g/mole</i>	2 mg/mL	1:10	1:1000	1
	1.8×10^{-3} M	1.8×10^{-4} M	1.8×10^{-6} M	
Rocuronium bromide <i>Molecular weight= 609.7 g/mole</i>	10 mg/mL	Undiluted	1:100	100
	1.6×10^{-2} M	1.6×10^{-2} M	1.6×10^{-4} M	

6. Testing

Table 8 continued.
Recommended testing concentrations

Vecuronium bromide <i>Molecular weight= 637.74 g/mole</i>	4 mg/mL 6.3x10 ⁻³ M	Undiluted 6.3x10 ⁻³ M	1:10 6.3x10 ⁻⁴ M	350
Pancuronium bromide <i>Molecular weight= 733 g/mole</i>	2 mg/mL 2.7x10 ⁻³ M	Undiluted 2.7x10 ⁻³ M	1:10 2.7x10 ⁻⁴ M	150
Morphine	-	1:10	1:1000	-
Opioids (other)	-	Undiluted	Undiluted	-
Hypnotics	-	Undiluted	Undiluted	-
Latex (commercial extract)	-	Undiluted	Not performed	-
Chlorhexidine	-	Undiluted	Undiluted	-
Antibiotics	-	Undiluted	Undiluted	-
Volume expanders	-	Undiluted	Undiluted	-

Footnote: all testing concentrations taken from the Société Française d'Anesthésie et de Réanimation (SFAR) recommendations for France (Prevention of Allergic Risk in Anesthesia, SFAR 2001).



Prick testing

Prick tests are performed by pricking the epidermis of the forearm with a needle through a drop of the test drug. The typical drug dilutions used range from 1 in 1 to 1 in 10. However, different dilutions are used in different countries and this poses a major problem when trying to compare results. Table 8 gives more details about

the recommended concentrations for various drugs.

The result should be read 15–20 minutes after administration. In many centres the criteria for a positive test are:

- wheal and/or flare is >3mm of negative control

OR

- wheal and/or flare is \geq half the diameter of the positive control.

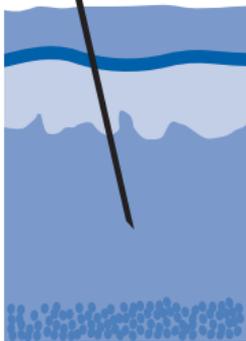
Prick tests, like intradermal tests, probably have a very low specificity. This could result in a major bias in the estimation of anaphylaxis to an agent if only skin tests are used.



Intradermal

Intradermal tests are performed by injecting a minute amount of drug (0.02–0.1mL) into the dermis of the forearm or the back. The typical drug dilutions used range from 1 in 100 to 1 in 10,000. Table 8 gives more details about the

recommended concentrations for various drugs.



As stated before, it is important to use the correct dilution when testing NMBAs. For example, intradermal testing with rocuronium and cisatracurium should be performed at concentrations lower than currently employed to avoid false positive responses.³² A more recent study suggests an even lower

concentration of at least 10^{-6} M and 10^{-7} M, respectively, or a dilution of approximately 1:1000.³⁴

The high incidence of positive responses to rocuronium in the French study occurred in patients tested with 1 in 10 dilutions (approximately 10^{-3} M) and may thus have included false positive responses.³²

More false-positive responses and cross-sensitivity occur with

6. Testing

intradermal tests than prick tests. However, for the patient, false positives are less serious than false negatives. Other potential problems with intradermal skin testing are shown in Table 9.

Table 9.
Problems with intradermal skin testing

1	Choice of test concentrations
2	Technique is challenging
3	Criteria for positive response are not well defined
4	Non-specific effects at higher concentrations, particular with histamine-releasing drugs but also with drugs that have a direct vasodilating effect
5	Predictive value is low
6	Questionable value for cross-reactivity with NMBAs – a larger dose is injected compared with prick testing
7	Sensitivity and specificity differs for each drug and test concentration – invalidates the method for comparing the results of different drugs

Prick versus intradermal skin testing

Prick testing is generally used as the initial test, followed by intradermal testing if the result is negative. Intradermal testing is performed as the initial test in some centres. Rare cases of anaphylaxis during intradermal testing have been described.

Larger volumes are used in intradermal testing and the results are considered by some to be more consistent. The threshold for direct mast cell degranulation or local vascular effects are being investigated and becoming better established for intradermal tests.

The prick test is easier to perform and causes the patient less discomfort than the intradermal test. However, since the prick test has been shown to give more false negatives, the intradermal test is the preferred method in many centres.

7. Treatment

The Association of Anaesthetists of Great Britain and Ireland has issued guidelines on the management of anaesthetic anaphylaxis. These guidelines are obtainable online at www.aagbi.org.uk. Some hospitals have implemented the availability of an 'anaphylaxis kit' in every operating theatre. It has also been suggested to post the action steps necessary in the event of a suspected allergic reaction on the theatre wall for easy reference.

Initial therapy

1. Call for help.
2. Stop administration of the drug(s) likely to have caused the reaction. It is recommended to stop all the drugs that are possible to stop, as at this time the causative agent can not be determined.
3. Maintain airway: give 100% oxygen.
4. Lie patient flat with feet raised.
5. Give adrenalin (epinephrine). This may be given im at a dose of 0.5–1.0 mg (0.5–1.0 mL of 1:1,000) and may be repeated every 10 minutes according to the arterial pressure and pulse until improvement occurs.

Alternatively, 50–100 µg iv over 1 minute (0.5–1.0 mL of 1:10,000) has been recommended for hypotension with titration of further doses as required. Never give undiluted epinephrine 1:1,000 intravenously.

In a patient with cardiovascular collapse, additional doses of epinephrine 0.5–1 mg iv (5–10 mL of 1:10,000) may be required 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 rapid iv volume expansion with crystalloid or colloid. If colloid has been given prior to the reaction, change to crystalloid because the causative agent might have been the colloid.
6. Save any blood samples that have been collected prior to or during the procedure. These may be required for testing.

7. Treatment

Secondary therapy

1. Antihistamines (chlorpheniramine 10–20 mg by slow iv infusion).
2. Corticosteroids (100–500 mg hydrocortisone iv).
3. Bronchodilators may be required for persistent bronchospasm.
4. Prolonged monitoring in the Intensive Care Unit.

Treatment

The management outlined here is based on the AAGBI guidelines.

Anaphylaxis avoidance

A vigilant and well-educated clinician can be the most important factor in avoiding anaphylaxis and if it does occur, its treatment.

The most important component of anaphylaxis management is prevention. It is easier to avoid non-allergic than allergic anaphylaxis. Prevention relies on accurate documentation of previous reactions and the avoidance of the offending drug(s).

Avoidance or prevention involves taking a history of allergy from the patient prior to anaesthesia administration. Typical questions would include the following:

- Is there a history suggestive of allergy (rash, hives, swelling of the face or throat, hay fever, asthma, eczema)?
- What does the patient think may have caused these symptoms?
- Has there been any allergic response to condoms, rubber gloves, children's balloons?
- Has the patient had previous general anaesthetics? Were there any problems?
- Has the patient ever had locoregional anaesthesia? Were there any problems?
- Does the patient take any medication?

If a history of drug allergy is identified, sensitivity testing for the agents that will be used during the anaesthetic may be warranted.

When administering an anaesthetic, the circumstances can be modified to reduce the possibility of untoward reactions by:

- giving the drug more slowly
- reducing the dose of the drug
- avoiding multiple drugs over a short period of time
- avoiding rapid epidural dosing
- taking care with patients on oral antihypertensives
- avoiding hypovolaemia
- using pre-operative H₁ and H₂ blocking agents and/or corticosteroids in susceptible patients and atopic individuals. However, this remains controversial.

However, although useful in some cases, this type of sensitivity testing is often unreliable for making an accurate assessment of risk.

Follow-up

In a patient who has experienced an anaphylactic reaction, the offending agent should be identified by thorough testing and subsequently avoided for future anaesthetics.

It is important that the procedures in the following checklist are performed because the number of cases where patients had a reaction without it being properly investigated and subsequently received the causative drug again is exceptionally high. It is also important that the adverse event is reported to the regulatory authorities (for the UK this is the Medicines and Healthcare Regulatory Agency, Yellow Card reporting on www.mhra.gov.uk) so that all drugs can be monitored as part of post-marketing surveillance. A copy of the adverse event report should be sent to the manufacturer. The patient should also be made aware.

Checklist of follow-up in the case of a suspected anaphylactic reaction during anaesthesia

Record the following information:

- Patient's details – patient number, date of birth, name and address
- Hospital
- Date and time of incident
- Detailed description of the incident, including copies of monitoring traces if available and an accurate timeline of events and drug administration
- Operation, including anaesthetic line insertion and urethral catheter, etc
- Names of the anaesthetists involved and all staff present
- All drugs, intravenous fluids and skin antiseptics administered concomitantly, as well as all drugs used for premedication and during anaesthesia
- Time when blood samples are taken
- Referral to regional allergy centre (if appropriate)
- Blood test results – tryptase, IgE tests, other
- Skin test results, concentrations used, controls used
- Immunologist's interpretation
- Explanation given to patient
- Incident recorded in hospital notes
- Primary care practitioner informed
- Other clinicians informed
- Adverse event reporting authority informed, copy of the report to the manufacturer
- Warning bracelet offered if indicated.

8. Summary

- Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction.
- The incidence of anaphylaxis during anaesthesia is very rare (approximately 1 in 20,000 anaesthetic procedures).
- Although NMBAs are generally thought to be the most common cause, anaphylaxis due to these agents is still a rare event. The incidence of anaphylaxis with NMBAs is low throughout the world.
- Other common causes during anaesthesia include latex, chlorhexidine, antibiotics and opioids.
- Differences in the reported incidence of anaphylaxis associated with individual NMBAs, is mainly due to differences in the test methods used and the relative market share of these agents between different countries.
- In the case of an anaphylactic reaction, rapid assessment is essential so that appropriate treatment can be given.
- In order to confirm the diagnosis and identify the causative agent, a number of different skin and blood tests must be performed.
- Testing must be carried out by an immunologist at a centre with experience of drug testing with these agents.
- Currently, testing procedures and reporting guidelines vary between centres and countries so it is difficult to compare the results. Ideally, there should be internationally agreed testing and reporting methods.
- There is no gold standard test. Even if every procedure is followed accurately, there will always be false negatives and false positives.
- Consistent monitoring, testing and reporting of suspected cases of anaphylaxis is needed.
- The actions that should be carried out in the event of an anaphylactic reaction are summarised in Table 11.

8. Summary

Table 11.

What to do in the event of an anaphylactic reaction

Action 1	Action 2	Action 3	Action 4	Action 5	Action 6
Immediate	Immediate	1 hour later	4–6 weeks or earlier	6–8 weeks	In the future
Call for help	Take blood sample for mast cell tryptase	Take second blood sample for mast cell tryptase	Skin tests IgE antibody tests	See patient with immunologist if possible to discuss the test results File written summary to Primary care practitioner/ surgeon and case notes Report the adverse event to the authorities and the company Offer the patient a warning bracelet	As immunology centres link up nationally and internationally, the record should be held on file
Stabilise patient	Save any blood samples that have been taken prior to or during the procedure				

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10. Glossary

Allergy: a hypersensitive state acquired through exposure to a specific antigen, re-exposure bringing to light an altered capacity to react.

Anaphylaxis: a severe, life-threatening, generalised or systemic hypersensitivity reaction.

Antigen: any substance that is capable of inducing a specific immune response and of reacting with the products of that response.

Atopy: the tendency to produce specific IgE antibodies to one or more of the common allergens, e.g. house dust mite, grass pollen and animal dander.

Hyper-reactivity: an exaggerated normal response to a stimulus.

Hypersensitivity: a state of altered reactivity in which the body exhibits an exaggerated immune response to a foreign agent.

IgE antibody: one of a series of proteins with known antibody activity, synthesised by lymphocytes and plasma cells and found in serum and body tissues. It is involved in immediate hypersensitivity reactions. 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.

Mast cell tryptase: a major protein in mast cell granules, which is released together with histamine and other amines in anaphylactic reactions.

RAST (radio-allergosorbent test): a technique for measuring antigen-specific IgE antibodies in serum. The CAP system (Pharmacia) is an alternative to RAST and is a fluoro-immunoassay.



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