Introduction

Allergic reactions during anaesthesia often represent a diagnostic challenge due to the circulatory and respiratory effects of the anaesthetic drugs masking the symptoms of anaphylaxis. A successful outcome depends on prompt diagnosis and correct treatment of the reaction [1]. All drugs and substances used during the conduct of anaesthesia have the potential to cause allergic reactions. Reactions to individual drugs are, however, rare and attention should be focused on ensuring that anaesthetists can diagnose and treat anaphylaxis during anaesthesia. Following successful treatment of a suspected allergic reaction during anaesthesia investigations should be undertaken to determine the cause of the reaction, with the aim to prevent subsequent exposure. Due to the nature of these investigations, they should be conducted in specialist centres that possess both anaesthetic and allergist’s expertise. Only a few countries such as France, Australia, Norway, the United Kingdom and Denmark have such specialised anaesthesia-allergy centres.

Definition and incidence

Many different terms such as anaphylactic, anaphylactoid, pseudo allergic, histaminoid and so forth, can be found in the literature, reflecting individual differences in definition and underlying mechanisms. As this terminology has proved to be confusing a new classification has been proposed and the broad term ‘hypersensitivity reaction’ has been introduced [2]. Hypersensitivity reactions can be divided into allergic and non-allergic hypersensitivity reactions. Allergic hypersensitivity reactions can be further subdivided into IgE-mediated and non-IgE-mediated reactions. Anaphylaxis is used as an overall term for severe, generalised and life-threatening reactions, and is classified into the same categories as allergic hypersensitivity reactions. Most reactions associated with anaesthesia are allergic hypersensitivity reactions. In this article, for the sake of simplicity, allergic reaction will be used to describe these reactions whereas anaphylaxis will be used when describing severe life-threatening reactions.

Allergic reactions during anaesthesia are rare although the true incidence is difficult to estimate due to underdiagnosis, under reporting and differences in investigation and definition. The estimated incidence of allergic reactions during anaesthesia, based on referrals to anaesthetic allergy centres, ranges between 1:1 250 and 1:13 000 anaesthetics [3]. A recent prospective study conducted over two years in France, involved routine follow-up by an allergist of all adverse events or reactions associated with 70 000 anaesthetics. The incidence of hypersensitivity reactions in this hospital was reported to be 1:3 180 anaesthetics [4].

Causes

All drugs and substances used during anaesthesia and surgery have the potential to cause allergic reactions. Neuromuscular blocking agents (NMBA’s), latex, antibiotics, hypnotics, analgesics, disinfectants (for example, chlorhexidine), dyes (for example, patent blue), colloids and even sterilising agents (for example, ethylene oxide) have been implicated. Reactions to local anaesthetics are rarely allergic in nature, but more often due to vasovagal reactions or accidental intravascular injection. Geographical variations do exist, and in countries such as France, Australia, Norway and the United Kingdom, NMBA’s are by far the most common causes of allergic reactions. In Denmark a different pattern of causative agent is seen with the majority of cases being due to chlorhexidine, latex and antibiotics, largely reflecting their widespread use during anaesthesia and surgery.
NMBA’s and the pholcodine hypothesis

Although the use of NMBA’s is exclusively confined to general anaesthesia, reactions to these drugs can seemingly occur without prior exposure. This has led to a hypothesis of a possible cross-sensitising substance which could sensitise patients to NMBA’s in the absence of direct exposure to NMBA’s themselves. This theory was first proposed in 1983 when it was suggested that the quarternary ammonium ion could be such an agent [5]. The quarternary ammonium ion is present in a large number of foods, household chemicals, disinfectants and industrial materials.

More recently, differences in NMBA sensitisation in Norway, where the incidence is high, and in Sweden, where the incidence is low, were investigated in a study seeking specific antibodies against morphine and suxamethonium, both of which contain a quarternary ammonium ion. The antibodies were detected more commonly in Norwegian blood donors and allergic patients [6]. Subsequently a search was conducted to identify the drug or compound that could have caused the sensitisation to the quarternary ammonium ion in Norwegians. Pholcodine, a constituent of a cough medicine, marketed widely in Norway, but not in Sweden, was suspected to be the sensitising agent. The resultant ‘Pholcodine hypothesis’ suggested that the consumption of drugs containing pholcodine could lead to increased prevalence of IgE antibodies not only to pholcodine, but also to morphine and suxamethonium, leading to an increased risk of anaphylaxis to NMBA’s due to cross-reactivity. A multicentre study followed and investigated the prevalence of IgE to pholcodine, morphine and suxamethonium in atopic patients. In France and Norway, a relatively high prevalence of anaphylaxis to NMBA’s mirrored a high consumption of pholcodine and the relatively high percentage of atopic patients with IgE to pholcodine. In Denmark and Sweden, where relatively few reactions to NMBA’s were reported, pholcodine is not marketed commercially and no, or very few, patients had IgE antibodies to pholcodine [7].

Mechanisms

The clinical presentation and management of suspected allergic reactions during anaesthesia is the same regardless of the underlying mechanism. IgE-mediated allergic reactions occur when the allergen causes cross-bridging of the high affinity specific IgE receptors on the surface of mast cells leading to degranulation and release of vasoactive mediators. Non IgE-mediated allergic reactions and mast cell degranulation can also be triggered via IgG, C5a and C3a, neuropeptides and certain drugs [8]. Non-allergic reactions can be caused by direct pharmacological or ‘toxic’ stimulation of mast cells or basophils [2]. Determining the exact mechanism responsible is helpful in order to offer advice for the conduct of future anaesthesia. In cases where a drug is testing positive in several different test modalities and an IgE-mediated reaction is suspected, future exposure to that drug should be avoided because the risk of future reactions is high. On the other hand, most opioids are known to cause non-specific direct histamine release from mast cells and these reactions can usually be prevented by slow injection and pretreatment with antihistamines [9].

Clinical signs and symptoms

Signs and symptoms of allergic reactions developing during anaesthesia include any combination of cardiovascular, respiratory, skin or gastro-intestinal manifestations, similar to allergic reactions that occur outside the operating theatre. However, skin symptoms are often hidden by surgical drapes and gastro-intestinal symptoms will not necessarily be apparent in the anaesthetised patient. Respiratory, circulatory and cutaneous signs can be difficult to distinguish from ‘normal’ reactions to anaesthetic drugs or airway management. The severity of presenting symptoms may range from a mild rash observed postoperatively to cardiovascular collapse or severe bronchospasm, occurring at induction of anaesthesia, which is resistant to the usual treatments. In cases of circulatory compromise cutaneous signs may only appear once sufficient circulation has been re-established. The severity of reactions can depend on the mechanism causing the reaction, the allergen and the route of administration of the allergen. IgE-mediated reactions to drugs administered intravenously are more commonly associated with rapidly progressing severe hypotension than non-IgE mediated reactions [10].
Treatment

When allergic reactions occur during anaesthesia the patient will usually be fully monitored, intravenous access will have been established and anaesthetic personnel specially trained in emergency situations are already in attendance. This should provide optimal conditions for prompt treatment once anaphylaxis has been diagnosed. Treatment depends on the clinical severity of the reaction. For severe reactions with cardiovascular or respiratory involvement first line treatment is intravenous adrenaline starting with bolus doses of 0.01-0.05 mg (10-50 µg) titrating to effect. In cases of cardiovascular collapse bolus doses should be increased to 0.1-0.2 mg (100-200 µg) and an intravenous infusion of adrenaline should be considered [1]. Oxygenation should be maximized by securing the airway and giving 100% oxygen. Elevating the legs and administering intravenous fluids should ensure sufficient circulation in addition to the vasoconstricting effects of adrenaline.

Anaphylaxis can be difficult to diagnose during anaesthesia and this can lead to delays in treatment that may be detrimental. Therefore, anaphylaxis should be considered in the differential diagnosis of cases of circulatory instability unresponsive to the usual manoeuvres such as ephedrine, phenylephrine, fluid administration and elevation of the patient’s legs after a maximum period of 10 minutes [11]. If no other obvious cause is present and anaphylaxis cannot be ruled out, the immediate treatment should be intravenous adrenaline starting at 0.01 mg (10 µg) and titrating to effect. As adrenaline is a lifesaving, but also an extremely potent drug with potentially lethal side-effects [10, 12] all anaesthetists should be trained in the correct dilution and administration of adrenaline.

Intravenous antihistamines and steroids should be administered as second-line treatment and have a role in reducing skin symptoms and preventing relapse of anaphylaxis which can occur within 24 hr. In mild reactions limited to skin symptoms or swelling of the face or extremities, antihistamines and steroids can be administered as first-line treatment as long as the patient is observed closely for symptom progression. Continuation or cancellation of the surgical procedure and postoperative observation depend on the severity of the reaction and the response to treatment. Referral for allergy investigation should always be considered and the patient should be informed of referral.

When anaphylaxis occurs outside the operating theatre the allergen can often be identified. In this situation exposure is often to a single agent, for example an insect sting or injectable medication in a pre-hospital setting or in a general hospital ward. The diagnosis can be made swiftly and reliably in most cases and the recommended first-line treatment of anaphylaxis in this setting is intramuscular adrenaline 0.3 mg (300 µg) [13, 14]. The rationale for this is adrenaline at this dose and route is a reasonably safe treatment in an unmonitored patient without intravenous access. This approach mirrors the treatment of patients known to develop anaphylaxis following exposure to insect venom or peanuts for example, and in contexts such as this, adrenaline is often self-administered.

Diagnosis and investigations

Serum tryptase

In some cases the clinical reaction observed is highly suggestive of anaphylaxis, but in many cases the diagnosis is more difficult to make. When IgE-mediated reactions occur, serum tryptase is released from mast cells together with histamine and other mediators, and this has proven to be a useful marker in suspected allergic reactions during anaesthesia.

Serum tryptase peaks between 30 minutes and 2 hr after a reaction, accordingly a blood sample should be taken 30 minutes to 3 hr after the reaction. Tryptase levels correlate with severity of hypotension and in the case of severe reactions tryptase can be elevated up to 24 hr after the reaction [1]. As serum tryptase is very stable over several days it can be stored at room temperature and sent for analysis once the patient has been stabilised. To enable correct interpretation of the serum tryptase value it is very important to record both the time of blood-sampling and the time of the reaction accurately. Serum tryptase should always be compared with a baseline sample taken several days after the reaction has subsided. There is little variation in basal level serum tryptase in individual patients, therefore even a relatively small increase of more than 2.2 µg/l from the baseline value can be significant, even when the normal reference value is less than 11.4 µg/l [15].
Postoperative investigation

When patients are referred for investigation following a suspected allergic reaction during anaesthesia it is important to collect detailed information about the reaction regarding timing, symptoms, treatment and the response to treatment. Information from previous or subsequent anaesthetics is often also relevant. When deciding a plan of investigation, all drugs and substances used prior to the reaction should be considered. The lack of a single gold standard test to investigate these reactions usually means that several different test modalities are combined, with the purpose of increasing sensitivity and avoiding false negative test results, which may put the patient at risk during subsequent anaesthesia. The accompanying fall in specificity is usually acceptable, as a false positive test result will lead to a restriction in the choice of drugs for subsequent procedures, which is rarely likely to cause a problem.

The investigation of suspected allergic reactions during anaesthesia is a specialised and time consuming process. Currently only a minority of countries have a standardised test protocol and even fewer have centres dedicated to the investigation of these reactions. Investigations are based on a combination of blood tests (serum tryptase, specific IgE, basophil activation tests), skin tests (skin-prick tests, intradermal tests). In the Danish Anaesthesia Allergy Centre (DAAC) systematic drug provocation testing is also included in routine investigations.

When interpreting the results of any investigation, all test results are reviewed in the context of the observed clinical reaction to ensure the conclusions are consistent. Patients should be informed of the results and their significance and, where a specific cause is found, a warning card should be given to the patient. In addition, patients investigated in the DAAC are issued with a detailed letter describing the reaction that led to referral including symptoms, drugs given and treatment. Information on test results and conclusions of investigations are also included in the letter.

This has proven very useful especially in cases where no cause was found for the reaction. In many cases there are other plausible explanations for hypotension or bronchospasm and common non-allergic differential diagnoses include major haemorrhage, hypovolaemia, concomitant use of tricyclic antidepressants or ACE-inhibitors, exaggerated physiological response to oxytocin and poorly treated or undiagnosed asthma.

Prevention

The risk of future allergic reactions during anaesthesia is increased in patients with a previous reaction [16]. If investigations have taken place and a cause found, subsequent anaesthesia should avoid the causative agent and will usually be uneventful. If no cause was found and the reaction was thought to have an allergic mechanism pretreatment with antihistamines and steroids is usually recommended. However, there is no high level evidence for a preventative effect of pretreatment and due to the rare, unexpected and life-threatening nature of anaphylaxis it is unlikely that a high level of evidence will ever be available in this area [1].

If patients have experienced previous reactions but have not been investigated or for those patients where no specific cause was found, avoidance of suspected substances can be warranted. Guessing the cause of allergic reactions during previous anaesthesia can be hazardous and the recommendation is to avoid all drugs and substances administered prior to a reaction [17]. Anaesthetists should be ready to diagnose and prepared to treat anaphylaxis promptly. Recently published Scandinavian guidelines include a flow chart for the management of patients with a previous history of a serious reaction during anaesthesia [1].

Many patients report ‘allergies’ to various drugs and substances during the pre-anaesthetic visit, but the majority of these are non-allergic hypersensitivities such as nausea and vomiting from morphine, diarrhoea from penicillin or a bloated feeling from taking paracetamol. Proven allergy to one or more drugs is rare and does not increase the risk of a reaction during anaesthesia, unless potential cross-reactive drugs are administered. A number of patients report allergy to local anaesthetics, which on further detailed questioning can often be attributable to a vasovagal reaction or the effect of accidental intravascular injection of either the local anaesthetic itself or the adrenaline vasoconstrictor element that it may contain. True allergy to local anaesthetics is very rare, but the suspicion of an allergy can present a diagnostic dilemma for the anaesthetist, especially in cases of emergency Caesarean sections conducted under regional anaesthesia where local anaesthetics are required. The potential medico-legal consequence of giving a local anaesthetic to a patient who claims to have an allergy has to be weighed up against the risk of complications of a general anaesthetic in a non-fasting patient with a high risk of difficult intubation, aspiration etc. If appropriate, pre-operative testing with local anaesthetics can be warranted. Conversely,
some patients may not volunteer information suggestive of an undiagnosed latex allergy, such as itching from wearing rubber gloves or swollen lips from blowing up balloons, as they may not consider these to be relevant in the anaesthetic setting [4]. These patients, if not identified pre-operatively, may subsequently react to latex during surgery. The notion of merely asking the patient if they have any allergies may lead to missing or misleading information. Importantly anaesthetists should attempt to identify symptoms of allergy and phrase their questions accordingly: ‘Have you ever experienced itching of the skin, eyes, throat or nose?’ and ‘Have you ever had a rash or swelling of any part of the body after contact with or ingestion of food or drugs?’

Specific questions to establish allergic symptoms on exposure to antibiotics, latex or disinfecting agents are also useful. Patients volunteering that they are ‘allergic to anaesthesia’ have in most cases either suffered severe PONV or had a long stay in recovery due to the effects of the premedication, the anaesthetic or postoperative pain relief. These patients obviously need reassurance and education that these are not allergic symptoms.

There is no evidence to consider avoiding drugs that have been labelled as ‘high risk’ by word of mouth in the anaesthetic community. A florid debate concerning the risk of reactions associated with the NMBA rocuronium was conducted in the international literature some years ago [18, 19]. The overall risk of allergic reactions during anaesthesia is very low, even for NMBA’s in countries with a higher prevalence of these allergies. In Norway for example when NMBA’s have been used as part of the anaesthetic technique, the incidence of reactions to these drugs has been calculated to be 1:5 200 anaesthetics [20]. All drugs and substances can potentially cause anaphylaxis during anaesthesia and reactions will occur unexpectedly. The focus should, therefore, be redirected from incriminating single drugs or drug-groups in favour of improving awareness about the diagnosis and treatment of allergic reactions.

Key learning points

• Anaphylaxis during anaesthesia is rare, but can be difficult to diagnose.
• Anaphylaxis should be suspected in cases of severe hypotension refractory to usual treatments with ephedrine and fluids, if no other apparent cause can be found.
• First line treatment for anaphylaxis (reactions with circulatory and/or respiratory symptoms) is bolus doses of intravenous adrenochrome starting at 0.01-0.05 mg (10-50 µg) and titrating to effect.
• Serum tryptase can help confirm anaphylaxis and a blood sample should be taken between 30 minutes and 3 hr after the reaction.
  The time of sampling in relation to the reaction should be noted. Values should always be compared with a baseline taken at a later date.
• Patients should be referred for postoperative allergy investigation to determine the cause of the reaction. Such investigation is highly specialised and ideally should be conducted with co-operation between anaesthetists and allergists.

References