Allergic reactions during anesthesia: diagnosis and treatment

Filiep M. Soetens[1]
Marcel P. Vercauteren[2]

The term "anaphylaxis" is composed by "a na", meaning "not or contrary to" and "phylaxis", meaning "protection". Thus repeated exposure to a toxin may cause harm instead of prophylaxis or immunization.

An anaphylactic reaction or anaphylaxis is an immediate type hypersensitivity reaction to a substance or drug, causing acute life-threatening symptoms in two or more organ systems. Immunoglobulin IgE antibodies are involved. The reaction is independent of the pharmacological actions and the dose of the substance or drug. An anaphylactoid reaction is clinically indistinguishable from an anaphylactic reaction, but is not mediated by IgE antibodies. As a consequence a definite diagnosis can only be made after investigation (7,17,18,23,25,30,34,38). Before investigation of a reaction the term "suspected anaphylactic reaction" should be used (36-38). However, in the literature there is a lot of confusion about the terminology (28) while during last years it has been suggested to abandon the term anaphylactoid.

During anesthesia many different drugs are used in rapid succession: not only anesthetics, but also antibiotics, fluids, nonsteroidal anti-inflammatory drugs and other compounds (e.g. disinfectants, latex etc.). Most of them are given intravenously and in bolus, bypassing the body's primary immune filters and presenting high concentrations of antigen directly to the mast cells and basophils. So it is difficult to say which drug caused the suspected reaction or that the reaction was the result from the additive side effects of several drugs injected simultaneously (40).

1 Sint-Elisabeth Hospital, Turnhout, Belgium
2 Antwerp University Hospital, Belgium

Pathophysiology

In a "classical" anaphylactic reaction previous contact with the drug is necessary. Anesthetics are haptens with low molecular weight being too small to stimulate immune responses themselves. Haptens are not antigenic unless conjugated to carrier molecules, mostly proteins. At least 2 antigenic determinants per molecule are necessary to evoke an immune response. On first exposure to an antigen, B-lymphocytes produce IgE antibodies which bind to high affinity receptors on the surface of mast cells and the basophils. Mast cells are located in the pericapillary tissues of various organs. Basophils are the circulating counterparts of the mast cells. On second exposure, the multivalent antigen causes bridging of two adjacent IgE antibodies causing degranulation of the mast cells and the basophils (17,23,30,34).

The concentration of cAMP will decrease while the intracellular concentration of Ca^{++} will increase due to increased permeability of the cell membrane for Ca^{++} and mobilization from intracellular Ca^{++} stores. This causes degranulation of preformed mediators and activation of phopholipase A_2, which liberates arachidonic acid from the cell membrane synthesizing new mediators.

Mediators can be divided in three groups, depending on the time they are liberated after stimulation of the mast cell and the basophil. There is an immediate release of the granule content: the most important preformed mediators are histamine, tryptase, heparin, eosinophil and neutrophil chemotactic factors. Within minutes newly synthesized inflammatory mediators from the cell membrane are liberated: leukotrienes via lipoxygenase pathway (LTB_4, LTC_4, LTD_4, LTE_4), prostaglandins via cyclo-oxygenase pathway (PGD_2) and platelet activating factor. Finally, for several hours cytokines are produced and liberated (7,17,18,23,28,30,34).

The effects of these mediators are: decreased myocardial contractility, increased heart rate, coronary and pulmonary vasoconstriction, peripheral vasodilatation, increased hepatic venous resistance with pooling of blood in the splanchnic system, increased permeability (with up to 40% loss of intravascular fluid), smooth muscle contraction in the bronchi and the gastro-intestinal tract, increased mucus production, stimulation of sensory nerve endings and attraction of other inflammatory cells. In addition, these mediators and inflammatory cells activate the coagulation, the complement and the kinin-kallikrein pathway (7,14,17,18,23,28,30,34).

In an anaphylactoid reaction IgE antibodies are not involved. Previous contact with the drug is not required. The mechanism of mast cell and basophil degranulation is either non-immunologic histamine release or acti-

vation of the classical or alternate pathway of complement with the production of anaphylatoxins (C_{3a}, C_{4a} and C_{5a}) (7,17,18,23,28,30,34). Besides releasing mediators from mast cells and basophils, anaphylatoxins increase vascular permeability, contract smooth muscle and attract, aggregate and activate leukocytes and platelets (23). Non-immunologic or direct histamine release will primarily affect the mast cells; the most important mediator is histamine, which is liberated in a dose dependent fashion (23). The clinical effects are usually mild (33). However, some individuals (called „super-responders") release more histamine than normal in response to some drugs or have an exaggerated hemodynamic response to histamine (7). Moreover, mast cells of different organs react differently on different drugs (27). Most drugs release histamine from the mast cell of the skin, which is harmless. However, some drugs, like atracurium and propofol, also release histamine from the lung mast cell. Only atracurium releases histamine from the mast cell of the heart. In addition vecuronium inhibits N-methyltransferase, the enzyme that breaks down histamine (13). Combination of drugs can amplify the degranulation of the mast cell or intensify the effects of the degranulation and lead to an anaphylactoid reaction in a susceptible patient (7,25).

Epidemiology

The incidence of an anaphylactic reaction during anesthesia is between 1:3.500 and 1:20.000 (17,18). Adults, and more likely females, between 40 and 49 years are the most affected age group (31). There is a geographical variation in the incidence; it is lower in the USA and South Africa and higher in France and New Zealand (7). However, it is difficult to calculate the exact incidence due to inaccuracies in recognizing and reporting anaphylactic reactions and differences in the definition and investigation of an anaphylactic reaction. Also, one can only get a rough estimation of the amount of drugs sold or number of anesthetics done. Mortality of a suspected anaphylactic reaction is between 3 - 5% (17,18,30).

In France there is an allergy network (Groupe d"Etudes des Réactions Anaphylactoïdes Peranesthésiques, GERAP), coordinated by Laxenaire et al. (22,31). In 1999 and 2000 they investigated nearly 800 patients (31). Sixty-six percent of the reactions were anaphylactic and 34% of the reactions were anaphylactoid. Having a closer look at the anaphylactic reactions, 60% were caused by neuromuscular blocking drugs (NMBDs), followed by latex and antibiotics (both 15%). The incidence of anaphylactic reactions to **NMBD**s is 1 in 6.500, which is by far the highest of all the anesthetics (17). More than 50% of these reactions occur after the first exposure, which

seems contradictory to the mechanism of an anaphylactic reaction. There is a strong female predominance; a female: male ratio ranging from 2:1 to 8:1. Cross-reactivity between NMBDs occurs at about 70% (17,18,30). The antigenic determinant is probably the quaternary ammonium ion, which is the structure that binds the acetylcholine receptor (1). Quaternary ammonium compounds are abundantly present in drugs, cosmetics and household products. Individuals, especially females, could get sensitized to NMBDs by contact to cosmetics and household products and develop an anaphylactic reaction on first exposure to NMBDs. Most NMBDs have 2 quaternary ammonium ions and as a consequence two antigens. Therefore one NMBD can bridge two IgE antibodies and cause mast cell and basophil degranulation. Although small molecules as used in anesthesia require a protein carrier to become antigenic, NMBDs are an exception. This explains why NMBDs have the highest incidence of all anesthetic drugs. Among the NMBDs, succinylcholine has the highest incidence, probably because the chain between the two quaternary ammonium ions is very flexible, contrary to the other NMBDs who have a more rigid backbone between the 2 quaternary ammonium ions. The distance between the two quaternary ammonium ions is critical (17,18,30). There is a lot of controversy about the increased incidence of rocuronium in some countries (France and Norway) when compared with other NMBDs (16,22,31,35).

NMBDs can also cause anaphylactoid reactions. Benzylisoquinolinium NMBDs (e.g. atracurium, mivacurium and to a much lesser extent cisatracurium) may induce non-immunologic histamine release more often than aminosteroid NMBDs (e.g. pancuronium, vecuronium and rocuronium).

Latex causes IgE mediated reactions. Symptoms occur 30-60 min after the start of the procedure rather than at induction and there is no relation with any drug administration (15). Health care workers and patients with atopy, asthma, spina bifida, spinal cord injury, allergy to tropical fruits or multiple prior surgical procedures are at risk for an anaphylactic reaction to latex (17,18,30). Due to latex-free equipment the incidence is progressively decreasing. Patients at risk should be operated first time in the morning.

The incidence of reactions upon **thiopental** is about 1 in 30.000. In contrast with NMBDs, there is mostly a previous exposure. Thiopental can also cause anaphylactoid reactions by complement-activation. Propofol may cause anaphylactic and anaphylactoid reactions. Etomidate, ketamine and midazolam cause no or extremely rare reactions (17,30).

Anaphylactic reactions to **opioids** are extremely rare. However, non-immunologic histamine release is rather frequent, especially with codeine, morphine and meperidine. The mast cells of the skin, more than in other

organs, are extremely sensitive to opioids and therefore cause harmless reactions (17, 30).

Reactions to **local anaesthetics** are rare. Of the 205 patients referred to an allergy clinic for a suspected anaphylactic reaction to local anesthetics, only 4 had an anaphylactic reaction and 4 had delayed allergic reactions (9). Most of the alleged allergic reactions were caused by toxicity and/or adrenaline, vasovagal reactions or reactions to preservatives (e.g. [methyl]-paraben, meta-bisulphites) (30).

Symptoms and Diagnosis

In more than 90% of the cases (latex is an exception) symptoms start within 5-10 min after induction of anesthesia (23). Although anaphylactic and anaphylactoid reactions are clinically indistinguishable, the symptoms and signs of anaphylactic reactions tend to be more severe (30). The involved target organs are the skin, the respiratory, the cardiovascular and the gastrointestinal system (Table 1). The full range of clinical manifestations does not occur in every patient (17,18,23,30).

The incidence of cardiac arrest is about 10%. Cutaneous symptoms may be recognized in 70% of the cases. This also means that they were absent in 30%, possibly because the patients were anesthetized and under drapes. This is in contrast with anaphylaxis in the non-anesthesia setting where the incidence of cutaneous symptoms is higher. Bronchospasm is almost inevitable in patients with pre-existing asthma and may be the worst feature in 20% of the cases. For obvious reasons gastrointestinal features are uncommon during anesthesia. The most common initial feature during anesthesia is absence of pulse, oxygen desaturation, difficulty to ventilate the lungs and flushing.

Factors that increase the severity of the reaction are a history of asthma, use of β-adrenergic blocking drugs and neuraxial anaesthesia. All of these states are associated with a reduced efficiency of the endogenous catecholamine response. In the study of Jacobsen on an anesthesia simulator, making a correct diagnosis during the first 10 min of anaphylaxis seems to be difficult (19).

Treatment

The goals of the management of anaphylaxis are: interrupting contact with the responsible drug, modulating the effects of the released mediators and preventing more mediator production and release (17,18,23,25,30). Table 2 summarizes the management of a suspected anaphylactic reaction.

Table 1. Clinical manifestations of a suspected anaphylactic reaction

Organ system	*Symptom*	*Sign*	*Specific sign during anesthesia*
Cutaneous	*Itching*	*Goose-Flesh* *Rash, Erythema, Flushing* *Urticaria* *Periorbital and Perioral Oedema*	
Respiratory	*Lump in the Throat* *Hoarseness* *Dysphonia* *Dyspnoea*	*Stridor (Laryngeal Oedema)* *Wheezing (Bronchospasm)* *Pulmonary Oedema* *Cyanosis*	*Difficult to Ventilate* *↑ Peak Airway Pressure* *↓ SaO_2* *↑ $EtCO_2$*
Cardiovascular	*Angina* *Light-headedness* *Faintness*	*Tachycardia* *Hypotension - Cardiac Arrest* *Dysrhythmias*	*↓ $EtCO_2$* *↑ Haematocrit*
Gastrointestinal	*Nausea* *Abdominal Pain*	*Vomiting* *Diarrhea*	

Table 2. The management of a suspected anaphylactic reaction

Initial Therapy:
1. Stop administration of the antigen and minimize inhaled anesthetics
2. Call for help; stop surgery
3. Endotracheal intubation and 100% O_2.
4. Volume expansion – leg elevation.
5. Adrenaline: 5 – 100 µg IV; closed chest cardiac compressions

Secondary Therapy:
1. Histamine 1 receptor antagonists: promethazine 50 mg IM
2. Histamine 2 receptor antagonists: ranitidine 50 mg IV
3. Catecholamine infusions
4. Nebulization of bronchodilators
5. Corticosteroids: hydrocortisone 5 mg/kg IV
6. Others: tranexaminic acid, glucagon, aminophyllin etc.

The initial therapy consists of discontinuing the administration of the suspected antigen to prevent further activation of the mast cells and basophils and to minimize the concentration of inhaled anesthetics, because they produce cardiovascular depression (23). Endotracheal intubation should be performed immediately if the airway appears to be at risk (e.g. stridor, oedema of the face or upper airway) (23). To compensate for the intravascular fluid loss, volume expansion is provided with colloids (allergy risk) or crystalloids. Leg elevation will increase the circulating volume with more than half a litre (17).

The cornerstone of successful therapy is adrenaline (17,18,23,25,29,30). Adrenaline counteracts some of the effects of mediator release: stimulation of the α1-adrenergic receptors constricts the capacitance and resistance blood vessels, stimulation of the β1-adrenergic receptors increases myocardial contractility and stimulation of the β2-adrenergic receptors dilates the smooth muscles of the bronchi, decreases hepatic venous resistance (and as a consequence increases venous return) and increases cAMP in the mast cells and basophils thus causing dephophorylation of myosin. An increase in cAMP decreases mediator release from mast cells and basophils. Because of its β-adrenergic effects adrenaline is more useful than the pure α-adrenergic agonists (e.g. noradrenaline). $CaCl_2$ is contraindicated because it increases intracellular Ca^{++} which promotes mediator release. The dose of adrenaline depends on the severity of the symptoms. For less severe reactions, adrenaline can be given intramuscularly in the lateral thigh in a dose of 10 µg/kg

(29). Intravenously, it is important to dilute and titrate adrenaline to avoid possible side-effects, like arrhythmias, hypertension and myocardial ischemia and infarction (29). If the patient is hypotensive, boluses of 5 to 10 μg of adrenaline are given every 1 to 2 min. In the case of cardiovascular collapse, boluses of 100 μg are administered every minute together with closed chest cardiac compressions (25). A higher dose of adrenaline is needed during anesthesia in comparison to the non-anesthesia setting, because both general and regional anesthesia impairs the sympathetic response. Patients taking β-adrenergic blocking drugs are more resistant to the effects of adrenaline and show unopposed α-adrenergic effects. Glucagon can be given 1-5 mg IV when available (25). Glucagon increases intracellular cAMP independent of the β-adrenergic receptors. In contrast, patients taking antidepressants (tricyclic antidepressants, monoamine oxidase inhibitors) and cocaine are more sensitive to the effects of adrenaline (29). Mortality of anaphylaxis increases if administration of adrenaline is delayed or used inappropriately in patients with asthma or cardiovascular disease and in the elderly (29).

After the initial therapy some other drugs, although less important, can be given, like histamine 1 receptor antagonists (promethazine IM). Histamine antagonists compete with histamine at the receptor sites (17,18,23,25,30). The use of histamine-2 receptor antagonists is controversial. Stimulation of the histamine-2 receptor has some beneficial effects: coronary vasodilation, stimulation of the myocardial contractility, bronchodilatation and a negative feedback on histamine release (25,28). The usefulness of corticosteroids in treating acute reactions is controversial, as they require 12-24 h to work. They inhibit phospholipase A_2, thus decreasing the mediators formed out of arachidonic acid (25). Other therapies are inhaled bronchodilators for persistent bronchospasm and catecholamines in infusion for persistent hypotension (25). Facial or scleral oedema and absence of an air leak after deflation of the cuff of the endotracheal tube suggest residual airway oedema (25). Extubation should be delayed in these cases.

Investigation of a suspected anaphylactic reaction

The goals of the investigation of a suspected anaphylactic reaction are (7,17,18,30):

1. Determine the nature of the reaction: is it an anaphylactic or an anaphylactoid reaction?
2. If the reaction is anaphylactic, identify the responsible drug.
3. If the responsible drug is a NMBD, determine if there is cross-reactivity between the NMBDs with the intention to find a safe NMBD for future anesthesia.

4. Investigation can be important for medico-legal reasons.

Investigation starts with a detailed clinical history, including the previous anesthetic history, previous allergies, the drugs used before and during the suspected anaphylactic reaction, severity of the symptoms and the timing of the drug administration in relation to the symptoms. Further investigation consists of intra- and postoperative tests. The intraoperative tests try to determine if the reaction is immune mediated. The postoperative tests try to identify the responsible ("culprit") drug (30).

Investigation: intraoperative testing

During the suspected anaphylactic reaction several mediators can be determined: histamine and mast cell tryptase (MCT) in serum and N-methylhistamine, a breakdown product of histamine, in urine.

Histamine is released from activated mast cells and basophils but undergoes rapid metabolism. As a consequence half-life is only a few minutes. The concentration of histamine peaks at 10 min and normalizes quickly. Therefore sampling needs to be done within 10 min after the onset of the reaction, at a time resuscitation of the patient is a priority (7,20,30).

MCT is a neutral protease and is only released from activated mast cells but not from basophils. The concentration of tryptase is 300-700 times higher in mast cells than in basophils. The half-life of MCT is 90-120 min. The concentration of MCT reaches its peak at 60 min and remains elevated for several hours. Sampling can be done after the initial resuscitation (7,20,30). It is recommended to take 3 samples: one immediately after the initial resuscitation, another 1 h after the start of the reaction at the (most important) moment the MCT concentration normally peaks and the last sample 24 h after the reaction to get a baseline value (38). Another advantage of MCT in comparison with histamine is that the sample is stable, easier to handle and not affected by hemolysis. It can even be taken postmortem (10,20). MCT is absent in normal serum and in serum obtained during septic shock and myocardial infarction (20). In a study of Fisher et al. IgE antibodies were found in 125 of the 130 patients with a raised MCT while IgE antibodies were found in seven of the 137 patients with a normal MCT level (10). Thus, an increased MCT concentration favors an anaphylactic reaction. A normal MCT concentration does not exclude an anaphylactic reaction and further investigation is necessary, certainly if there is a strong clinical suspicion of anaphylaxis although MCT may also be liberated with non-immunologic histamine release (39).

N-methylhistamine is a metabolite of histamine, which is excreted in the urine. The concentration of N-methylhistamine in urine remains elevated

longer than the concentration of histamine in serum. Nevertheless, sensitivity of this assay is very low and determination is no longer recommended (30).

Investigation: postoperative testing – skin tests

The injection of allergen in the skin causes bridging of 2 IgE antibodies and mast cell activation, which produces the typical wheal (oedema from increased capillary permeability) and flare (cutaneous vasodilatation) reaction. Most patients complain of itching (7,23,32). Skin tests need to be done 4-6 weeks after the suspected anaphylactic reaction. Before 4 weeks the intracellular stocks of histamine and other mediators are still lower than normal. As a consequence, the probability of a false negative result is greater. For the same reason drugs that could modify the response of the skin have to be avoided (e.g. anti-histamines, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, neuroleptics, vasoconstrictor etc.) (5). A positive control with histamine or codeine is done to test if the skin of the patient is able to react with a weal and flare reaction. A negative control with saline is done to exclude dermatographism (5). Skin tests are very valuable when investigating reactions to NMBDs, hypnotics and antibiotics, but have a limited value in reactions to colloids and contrast media (7).

In the intradermal skin test 0.01-0.02 ml of the diluted drug is injected in the dermis on the volar surface of the forearm with a 26-gauge needle to raise a weal of 1 - 2 mm (5,7). Some investigators inject more (0.05 ml) (32). The dilutions vary between 1:100 and 1:100,000 and are determined in healthy volunteers (5,7). In the skin prick test the undiluted drug is introduced in the epidermis by pricking the patient's skin through a drop of the drug to be tested. To avoid false positive results some drugs (e.g. atracurium, mivacurium and morphine) are diluted 10 times (30). An intradermal skin test is considered positive when the wheal has a diameter of 8 mm or more, surrounded by a flare (5,7,32). A skin prick test is considered positive when the weal has a diameter of 3 mm or more, surrounded by a flare (7,32). In both tests, the weal should arise within 10 min after injection and persist for more than 30 min. Both sensitivity and specificity are high: above 95% (32). False positive results are caused by non-immunologic histamine releasing drugs (e.g. atracurium) or by direct dilatation of the small blood vessels of the skin (e.g. rocuronium) (24). The incidence of adverse reactions is less than 0.3%. Thus, resuscitation facilities have to be available (5).

The intradermal skin test is said to be easier to perform for the infrequent user and has a proven reliability with time (the intradermal skin test stays positive for years) (6). The skin prick test is easier in preparation and thus

cheaper, causes less trauma and pain to the skin and can be used in children (32). If both tests are done, there is a more than 90% agreement between them facilitating to find the culprit drug (8,32).

It has been known for several years that the dilution of drugs for intradermal skin testing is critical in order to avoid false positive results (2,5,24). This probably also holds true for skin prick tests. Recently, Dhonneur et al found that in healthy volunteers skin prick tests to undiluted rocuronium and vecuronium resulted in 50% and 40% positive skin reactions, respectively (3). This could explain the differences in the incidence of anaphylactic reactions between centers and countries. International guidelines defining threshold concentrations for intradermal and skin prick testing are needed (3,26). Larger dilutions are recommended for atracurium, mivacurium and rocuronium.

Not only the drugs used during the suspected anaphylactic reaction should be tested, but also all other available anesthetics, especially NMBDs (5,7). The incidence of cross-reactivity between NMBDs is high. If a person has a positive skin test to one NMBD, the probability to react to another NMBD is 66% and to more than one other NMBD is 40%. The most frequent combinations are vecuronium with pancuronium and succinylcholine with aminosteroid NMBDs (7,11).

In patients with a history of anaphylactic reaction to a NMBD presenting for anesthesia, pre-treatment with antihistamines and steroids is not useful and could even be dangerous, because it can mask the early signs of the anaphylactic reaction (30). A NMBD that tested negative during skin testing should be used, although this is no absolute guarantee for prevention of an anaphylactic reaction (11,36,37).

Investigation: postoperative testing – other tests

Specific IgE antibodies

A radioallergosorbent test (RAST) determines antigen specific IgE antibodies in serum. This assay measures the circulating IgE antibodies in the assumption that it reflects the IgE antibodies bound to mast cells and basophils. The antigen is bound to a solid support and incubated with the patient"s serum. The serum is then washed away and radio-labeled anti-IgE antibodies are added. The amount of radioactivity is counted: high radioactivity means that the patient has specific IgE antibodies to the antigen (7). The concentration of specific IgE antibodies is the same during the reaction as after 4 - 6 weeks (21). So, if we need a fast result this test can be performed. Performing both skin testing and RAST for specific IgE antibodies, increases the incidence of finding the responsible drug with 5%. However,

RASTs for determination of specific IgE antibodies are only readily available for a limited number of drugs or substances (e.g. succinylcholine, latex). In addition, although the specificity is high, the sensitivity is low. Thus there are a lot of false negatives (23). Morphine has a single substituted ammonium group, which avidly binds to IgE antibodies specific to NMBDs. The morphine RAST was a more sensitive and specific test for the detection of IgE antibodies to NMBDs than specific NMBD RASTs (12).

Basophil activation test

When basophils are activated with a specific antigen, the membrane of the intracellular granules fuses with the cell membrane. The membrane of these intracellular granules is different from the membrane of the cell (e.g. CD63). This difference in composition can be measured by flow cytometric analysis. This test has several advantages: it is a simple test, gives a quick result, has a high specificity and it is positive in both IgE and non-IgE mediated reactions. The test has also several disadvantages: the sensitivity is only 66% and it can only be performed after 4 - 6 weeks in specialized centers (4).

The challenge test

Because of the risk of life-threatening reactions, challenge tests are not done except for local anesthetics. First, the local anesthetic is injected intradermally in increasing concentrations. If the intradermal skin test is negative with the undiluted concentration, the local anesthetic is injected subcutaneously (18, 30).

After the investigation we should inform the manufacturer and write a letter to the patient and the general practitioner (patients with an anaphylactic reaction as well as the ones with an anaphylactoid reaction). This letter should explain the event, describe the results of the tests performed and give recommendations about future anesthesia. To this letter the information of a future anesthesia should be added. The patient should be encouraged to wear a medic alert bracelet (7, 30).

Conclusions

Allergic reactions during anesthesia are rare, but potentially life-threatening allergic events. The worst manifestations are cardiovascular collapse, bronchospasm and laryngeal oedema. Anaphylactic and anaphylactoid reactions are clinically indistinguishable. The most incriminated agents are neuromuscular blocking drugs and latex. Treatment consists of instant interruption of contact with possible antigens, 100% oxygen, intubation, adrenaline and volume expansion. Cross-reactivity between neuromuscular blocking drugs occurs frequently. Further investigation is mandatory to find the responsible

drug and to make future anesthesia safe. Diagnosis is made with intraoperative tests (serum histamine and mast cell tryptase) and postoperative tests (skin tests and RASTs for specific IgE antibodies).

REFERENCES

1 Baldo B, Fisher M. Substituted ammonium ions as allergenic determinants in drug allergy. Nature 1983; 306: 262-4.
2 Berg C, Heier T, Wilhelmsen V, et al. Rocuronium and cisatracurium-positive skin tests in non-allergic volunteers: determination of drug concentration thresholds using a dilution titration technique. Acta Anaesthesiol Scand 2003; 47: 576-82.
3 Dhonneur G, Combes X, Chassard D, et al. Skin sensitivity to rocuronium and vecuronium: a randomized controlled prick-testing study in healthy volunteers. Anesth Analg 2004; 98:986-9.
4 Ebo D, Hagendorens M, Bridts C, et al. Allergic reactions occurring during anaesthesia: diagnostic approach. Acta Clinica Belgica 2004; 59: 34-43.
5 Fisher M. Intradermal testing after anaphylactoid reaction to anaesthetic drugs: practical aspects of performance and interpretation. Anaesth Intensive Care 1984; 12: 115-20.
6 Fisher M, Baldo B. Persistence of allergy to anaesthetic drugs. Anaesth Intensive Care 1992; 20 143-6.
7 Fisher M. Baldo B. Anaphylaxis during anaesthesia: current aspects of diagnosis and prevention. Eur J Anaesth 1994; 11: 263-84
8 Fisher M, Baldo B. Intradermal compared with prick testing in the diagnosis of anaesthetic allergy. Br J Anaesth 1997; 79: 59-63.
9 Fisher M, Bowey C. Alleged allergy to local anaesthetics. Anaesth. Intensive Care 1997; 25: 611-4.
10 Fisher M, Baldo B. Mast cell tryptase in anaesthetic anaphylactoid reactions. Br J Anaesth 1998; 80, 26-9.
11 Fisher M, Merefield D, Baldo B. Failure to prevent an anaphylactic reaction to a second neuromuscular blocking drug during anaesthesia. Br J Anaesth 1999; 82: 770-3.
12 Fisher M, Baldo B. Immunoassays in the diagnosis of anaphylaxis to neuromuscular blocking drugs: the value of morphine for the detection of IgE antibodies in allergic subjects. Anaesth Intensive Care 2000; 28: 167-70.
13 Futo J, Kupferberg J, Moss J, et al. Vecuronium inhibits histamine N-methyltransferase. Anesthesiology 1988; 69:92-6.
14 Gelman S, Mushlin P. Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. Anesthesiology 2004; 100: 434-9.
15 Gerber A, Jörg W, Zbinden S, et al. Severe intraoperative anaphylaxis to surgical gloves: latex allergy, an unfamiliar condition. Anesthesiology 1989; 71: 800-2.
16 Guttormsen A. Allergic reactions during anaesthesia – increased attention to the problem in Denmark and Norway. Acta Anaesthesiol Scand 2001; 45:1189-90.
17 Hepner D, Castells M. Anaphylaxis during the perioperative period. Anesth Analg 2004; 97: 1381-95.
18 Holzman R, Hirshman C. Anaphylactic reactions and anesthesia. In: Longnecker D., Tinker J., Morgan E. eds, Principles and practice of anesthesiology. 2nd edn., Saint-Louis, Mosby, 1998, p. 2385-405.
19 Jacobsen J, Lindekaer A, Ostergaard H, et al. Management of anaphylactic shock evaluated using a full-scale anaesthesia simulator. Acta Anaesthesiol Scand 2001; 45: 315-9.
20 Laroche D, Vergnaud M, Sillard B, et al. Biochemical markers of anaphylactoid reactions to drugs. Comparison of plasma histamine and tryptase. Anesthesiology 1991; 75: 945-9.
21 Laroche D, Lefrançois C, Gérard J, et al. Early diagnosis of anaphylactic reactions to neuromuscular blocking drugs. Br J Anaesth 1992; 69: 611-4.
22 Laxenaire M, Mertes P. Anaphylaxis during anaesthesia. Results of a two-year survey in France. Br J Anaesth 2001; 87: 549-58.
23 Levy J. The allergic response. In: Barash P., Cullen B., Stoelting R., eds, Clinical anesthesia. 2nd ed.., Philadelphia, J.B. Lippencott Company, 1992, p.1431-45.
24 Levy J, Gottge M, Szlam F, et al. Weal and flare responses to intradermal rocuronium and cisatracurium in humans. Br J Anaesth 2000; 85:844-9.
25 Levy J. Anaphylaxis: What is monitored to make a diagnosis? How is therapy monitored? Anesthesiol Clin North America 2001; 19: 705-15.
26 Levy J. Anaphylactic reactions to neuromuscular blocking drugs: are we making the correct diagnosis? Anesth Analg 2004; 98: 881-2.
27 Marone G, Stellato C, Mastronardi P, et al. Mechanisms of activation of human mast cells and basophils

by general anesthetic drugs. Ann Fr Anest Réanim 1993; 12: 116-25.
28 McKinnon R, Wildsmith J. Histaminoid reactions in anaesthesia. Br J Anaesth 1995; 74: 217-28.
29 McLean-Tooke A, Bethune C, Fay A, et al. Adrenaline in the treatment of anaphylaxis: what is the evidence? BMJ 2003; 327: 1332-5.
30 Mertes P, Laxenaire M. Allergic reactions occurring during anaesthesia. Eur J Anaesth 2002; 19: 240-62.
31 Mertes P, Laxenaire M, Alla F, et al. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999-2000. Anesthesiology 2003; 99, 536-45.
32 Moneret-Vautrin D, Kanny G. Anaphylaxis to muscle relaxants: rational for skin tests. Allerg Immunol 2002; 34: 233-40.
33 Naguib M, Samarkandi A, Bakhamees H, et al. Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine. Br J Anaesth 1995; 75: 588-92.
34 Roitt I, Delves P. Essential immunology, tenth edn., Blackwell Science, 2001.
35 Rose M, Fisher M. Rocuronium: high risk for anaphylaxis? Br J Anaesth 2001; 86: 678-82.
36 Soetens F, Smolders F, Meeuwis H, et al. Intradermal skin testing in the investigation of suspected anaphylactic reactions during anaesthesia – a retrospective survey. Acta Anaesth Belg 2003; 54: 59-63.
37 Thacker M, Davis F. Subsequent general anaesthesia in patients with a history of previous anaphylactoid / anaphylactic reaction to muscle relaxant. Anaesth Intensive Care 1999; 27: 190-3.
38 The association of anaesthetists of Great Britain and Ireland, Suspected anaphylactic reactions associated with anaesthesia. www.aagbi.org, august 2003.
39 Veien M, Szlam F, Holden J, et al. Mechanisms of nonimmunological histamine and tryptase release from human cutaneous mast cells. Anesthesiology 2000; 92: 1074-81.
40 Watkins J. Adverse reaction to neuromuscular blockers: frequency, investigation and epidemiology. Acta Anaesthesiol Scand 1994; 38 S 102: 6-10.