

Anaphylaxis during anaesthesia : diagnosis and treatment

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Summary : Anaphylactic and anaphylactoid reactions during anaesthesia 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. The incidence of cross-reactivity between neuromuscular blocking drugs is high. Further investigation of a suspected anaphylactic reaction is mandatory to find the responsible drug and to make future anaesthesia safe. Diagnosis is made with intraoperative tests (serum histamine and mast cell tryptase) and postoperative tests (skin tests and RASTs for specific IgE antibodies).

Key words : anaphylaxis ; skin testing ; anaesthesia : complications ; neuromuscular blocking drugs.

INTRODUCTION

The discovery of anaphylaxis goes back to the beginning of the 20th century. Richet and Portier studied the toxic dose of extracts of the sea anemone. In some dogs the first dose of toxin did not cause harm. However, the same dose of the toxin injected 3 weeks later, caused a quick and fatal systemic reaction with respiratory distress and diarrhoea. They called this reaction “anaphylaxis”, derived from the Greek words a(na), meaning “not or contrary to” and phylaxis, meaning “protection”. Thus repeated exposure to a toxin caused harm instead of prophylaxis or immunization. For this discovery Richet received the Nobel Prize in Physiology and Medicine in 1913 (17, 25, 34).

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 (Ig)E 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, 41). 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).

Anaesthesia is a unique situation for several reasons (41). Many different drugs are used in rapid succession : not only anaesthetics, but also antibiotics, fluids, nonsteroidal anti-inflammatory drugs and other compounds (e.g. disinfectants, latex...). Most of these drugs 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 anaphylactic reaction or that the reaction was the result from the additive side effects of several drugs injected simultaneously (40). Further investigation is thus necessary.

PATHOPHYSIOLOGY

In an anaphylactic reaction previous contact with the drug is necessary. Anaesthetics are low molecular weight molecules and are too small to stimulate immune responses themselves. They are haptens. 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. The IgE antibodies bind to high affinity receptors on the surface of the mast cells and the basophils. The mast cells are located in the pericapillary

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tissues of various organs. Basophils are the circulating counterparts of the mast cells. On second exposure, the multivalent antigen causes bridging of 2 adjacent IgE antibodies. As a consequence aggregation of the 2 IgE antibody receptors occurs and this causes degranulation of the mast cells and the basophils (17, 23, 30, 34).

Stimulation of the mast cell and basophil decreases the concentration of cAMP and increases the intracellular concentration of Ca^{++} , 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 phospholipase A_2 , which liberates arachidonic acid from the cell membrane. From arachidonic acid via different pathways new mediators are synthesized.

These 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 and eosinophil and neutrophil chemotactic factors. Within minutes newly synthesized inflammatory mediators from the cell membrane are liberated: leukotrienes via the lipoxygenase pathway (LTB_4 , LTC_4 , LTD_4 , LTE_4), prostaglandins via the 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 nonimmunologic histamine release or activation of the classical or alternative 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). The precise mechanisms of nonimmunologic or direct histamine release are not completely understood, but they primarily affect the mast cells; the most important mediator is histamine, which is liberated in a dose dependent fashion (23, 41). The clinical effects of nonimmunologic histamine releasing drugs are usually mild (33, 41). However, some individuals release more histamine than normal in response to some drugs or have an exaggerated haemodynamic response to histamine and have as a consequence an anaphylactoid reaction. These individuals are sometimes called "super responders" (7, 41). Moreover, mast cells of different organs react differently on different drugs (27, 41). 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 mast cell of the lung. 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 2 of these 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, 41).

EPIDEMIOLOGY

The incidence of an anaphylactic reaction during anaesthesia is between 1:3 500 and 1:20 000 (17, 18). Adults between 40 and 49 years are the most affected age group. Females are more likely than males to develop an anaphylactic reaction (31). There is a geographical variation in the incidence. The incidence 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, because there are potential problems with the numerator as well as with the denominator. Inaccuracies in recognizing and reporting anaphylactic reactions and differences in the definition and investigation of an anaphylactic reaction make it difficult to determine an exact numerator. Also, one can only get a rough estimation of the denominator by the amount of drugs sold or number of anaesthetics done (7, 41). The 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). This network gathers and investigates all suspected anaphylactic reactions and publishes the results on a regular basis.

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%). Reactions to hypnotics and opioids were rare. Other studies found about the same distribution of anaphylactic reactions (41).

The incidence of anaphylactic reactions to NMBDs is 1 in 6 500, which is by far the highest of all the anaesthetics (17, 41). Several observations are worth mentioning. First, more than 50% of these reactions occur after the first exposure, which seems contradictory to the mechanism of an anaphylactic reaction. Second, there is a strong female predominance with a female : male ratio ranging from 2:1 to 8:1. Third, there is a high incidence of cross-reactivity between NMBDs : about 70%. This means that if you react to one NMBD, there is a 70% chance you react to an other NMBD (17, 18, 30, 41). To get an answer to these observations we need to know what the antigenic determinant of the NMBDs is. 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. So one NMBD can bridge 2 IgE antibodies and cause mast cell and basophil degranulation. Small molecules, like anaesthetics and NMBDs, are normally not antigenic on their own. They need a protein carrier to become antigenic. NMBDs are an exception. This explains why NMBDs have the highest incidence of all anaesthetic drugs. Amongst 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, 41). Currently there is a lot of controversy about the increased incidence of

rocuronium in some countries (France, temporary Norway) when compared with other NMBDs (16, 22, 31, 35).

NMBDs can also cause anaphylactoid reactions. Benzylisoquinolinium NMBDs (e.g. atracurium, mivacurium) give nonimmunologic histamine release more often than aminosteroid NMBDs (e.g. pancuronium, vecuronium and rocuronium). Succinylcholine and cis-atracurium give the least nonimmunologic histamine release (17).

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). Patients with atopy, asthma, allergy to tropical fruits or multiple prior surgical procedures and health care workers are at risk for an anaphylactic reaction to latex (17, 18, 30, 41).

The incidence of thiopental causing anaphylactic reactions is about 1 in 30 000. In contrast with NMBDs, there is always a previous exposure. Thiopental can also cause anaphylactoid reactions. Propofol can cause anaphylactic and anaphylactoid reactions. Etomidate, ketamine and midazolam cause no or extremely rarely reactions (17, 30, 41).

Anaphylactic reactions to opioids are extremely rare. This is in contrast with nonimmunologic histamine release, which is frequent, especially with codeine, morphine and meperidine. The mast cells of the skin are extremely sensitive to opioids. The mast cells of the lung, the heart and gastrointestinal system and the basophils do not release histamine when exposed to opioids. As a consequence the reaction is restricted to the skin and is harmless (17, 30, 41).

Reactions to local anaesthetics are rare. Of the 205 patients referred to an allergy clinic for a suspected anaphylactic reaction to local anaesthetics, only 4 had an anaphylactic reaction to local anaesthetics and 4 had delayed allergic reactions (9). Most of the alleged allergic reactions were caused by toxicity of local anaesthetics and/or adrenaline, vasovagal reactions and reactions to preservatives (e.g. [methyl]-paraben, metabisulphites) (30, 41).

SYMPTOMS AND DIAGNOSIS

In more than 90% of the cases, symptoms begin within 5-10 min after induction of anaesthesia (23, 41). An exception is anaphylaxis to latex, which tends to occur 30-60 min after the start of surgery (15). Although anaphylactic and anaphy-

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 ↓ S _a O ₂ ↑ EtCO ₂
Cardiovascular	Angina Light-headedness Faintness	Tachycardia Hypotension - Cardiac Arrest Dysrhythmias	↓ EtCO ₂ ↑ Haematocrit
Gastrointestinal	Nausea Abdominal Pain	Vomiting Diarrhoea	

lactoid 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. The clinical manifestations of a suspected anaphylactic reaction are summarized in Table 1. The full range of clinical manifestations does not occur in every patient (17, 18, 23, 30, 41).

WHITTINGTON *et al.* described the incidence of the clinical features of anaphylaxis during anaesthesia in more than 500 patients (41). Cardiovascular collapse was the most common feature in 88% and the worst sign in 78% of the cases. The incidence of cardiac arrest was about 10%. Cutaneous symptoms were recognized in 70% of the cases. This also means that they were absent in 30%, possibly because the patients were anaesthetized and under drapes. This is in contrast with anaphylaxis in the non-anaesthesia setting where the incidence of cutaneous symptoms is higher. Bronchospasm was almost inevitable in patients with pre-existing asthma. Bronchospasm was the worst feature in 20% of the cases. Sometimes cardiovascular collapse or bronchospasm were the only signs of anaphylaxis, which made the diagnosis difficult. For obvious reasons gastrointestinal features were uncommon during anaesthesia (41). The most common initial feature during anaesthesia was absence of pulse, difficulty to ventilate the lungs and flushing (in 26%, 24% and 18% of the cases respectively) (41).

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 efficien-

cy of the endogenous catecholamine response (41). To make the correct diagnosis quickly, doesn't seem that easy. In the study of Jacobsen, none of the 42 anaesthesiologists tested on an anaesthesia simulator, made the correct diagnosis during the first 10 min of anaphylaxis (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, 41). Table 2 summarizes the management of a suspected anaphylactic reaction.

The initial therapy consists of discontinuing the administration of the suspected antigen to prevent further activation of the mast cells and basophils, and of minimizing the concentration of inhaled anaesthetics, 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 or crystalloids. Elevation of the legs will instantaneously increase the circulating volume with more than half a litre (17).

The cornerstone of successful therapy is adrenaline (17, 18, 23, 25, 29, 30, 41). Adrenaline counteracts some of the effects of mediator release: stimulation of the α_1 -adrenergic receptors constricts the capacitance and resistance blood vessels, stimulation of the β_1 -adrenergic receptors

Table 2

The Management of a Suspected Anaphylactic Reaction

<p>Initial Therapy :</p> <ol style="list-style-type: none"> 1. Stop Administration of the Antigen and Minimize [Inhaled Anaesthetics]. 2. Call for Help ; Stop Surgery. 3. Endotracheal Intubation and 100% O₂. 4. Volume Expansion – Leg Elevation. 5. Adrenaline : 5-100 µg IV ; Closed Chest Cardiac Compressions. <p>Secondary Therapy :</p> <ol style="list-style-type: none"> 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. Airway Evaluation before Extubation.

increases myocardial contractility and stimulation of the β_2 -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. 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. norepinephrine). CaCl₂ is contraindicated because it increases intracellular Ca⁺⁺, which promotes mediator release. The patients with respiratory difficulty and/or cardiovascular instability will benefit from adrenaline. The dose 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). If adrenaline is given intravenously, it is important to dilute and titrate adrenaline to avoid possible side-effects, like arrhythmias, hypertension and myocardial ischaemia 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 anaesthesia in comparison to the non-anaesthesia setting, because both general and regional anaesthesia impair the sympathetic response (41). Patients taking β -adrenergic blocking drugs are more resistant to the effects of adrenaline and show unopposed α -adrenergic effects. When available glucagon 1-5 mg IV can be given (25, 41). Glucagon increases intracellular cAMP independent of the β -adrenergic receptors. In contrast, patients taking antidepressants (tri-

cyclic antidepressants, monoamine oxidase inhibitors) and cocaine are more sensitive to the effects of adrenaline (29). Mortality of anaphylaxis increases if the administration of adrenaline is delayed, if adrenaline is used inappropriately, in patients with asthma or cardiovascular disease and in the elderly (29, 41).

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, 41). The use of histamine 2 receptor antagonists is controversial. Stimulation of the histamine 2 receptor has some beneficial effects : coronary vasodilatation, 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 too. Corticosteroids may require 12-24 h to work. Corticosteroids inhibit of phospholipase A₂, 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). After the reaction the patient can be extubated if there is no residual airway oedema. Facial or scleral oedema and absence of an air leak after deflation of the cuff of the endotracheal tube suggest residual airway oedema (25).

INVESTIGATION OF A SUSPECTED ANAPHYLACTIC REACTION

The goals of the investigation of a suspected anaphylactic reaction are (7, 17, 18, 30, 41) :

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 anaesthesia.
4. Investigation can be important for medico-legal reasons.
5. If the sample size is big enough, one can try to identify low and high-risk drugs.

Investigation starts with a detailed clinical history, including the previous anaesthetic 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 intraoperative and postoperative tests. The intraoperative tests try to determine if the reaction is immune mediated. The postoperative tests try to identify the responsible drug (30, 41).

INVESTIGATION : INTRAOPERATIVE TESTING

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

Histamine is released from activated mast cells and basophils. Histamine 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, 41).

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. After degranulation MCT diffuses from the connective tissues to the blood. 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, 41). The working party of the Association of Anaesthetists of Great Britain and Ireland on "suspected anaphylactic reactions associated with anaesthesia" advises to take three samples (38). One immediately after the initial resuscitation, another 1 h after the start of the reaction at the moment the MCT concentration normally peaks and the last sample 24 h after the reaction to get a baseline value. The sample taken 1 h after the start of the reaction is obviously the most important. Another advantage of MCT in comparison with histamine is that the sample is stable, easier to handle and not affected by haemolysis. 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). Increased MCT concentrations are highly suggestive of an anaphylactic reaction. In a study of FISHER *et al.* IgE antibodies were found in 125 of the 130 patients with a raised MCT (10). If the MCT concentration is not increased, the reaction was most probably anaphylactoid, although an anaphylactic

reaction cannot be ruled out completely. Again in the study of FISHER *et al.*, IgE antibodies were found in seven of the 137 patients with a normal MCT level (10). Thus, an increased MCT concentration favours 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. Some authors made the same observations. Others found that MCT was also liberated with nonimmunologic 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, the sensitivity of this assay is very low and determination is no longer recommended (30, 41).

INVESTIGATION : POSTOPERATIVE TESTING – SKIN TESTS

The cornerstone of postoperative testing are skin tests. The injection of allergen in the skin causes bridging of 2 IgE antibodies and mast cell activation, which produces the typical weal (oedema from increased capillary permeability) and flare (cutaneous vasodilatation) reaction. Most patients complain of itching (7, 23, 32, 41). 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. antihistamines, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, neuroleptics, vasoconstrictors...) (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). There are two types of skin tests : the intradermal skin test and the skin prick test.

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 of the

Table 3
Drug Dilutions used for Intradermal Skin Testing

Drug	Concentration in vial	Dilution for skin testing
Histamine	1 mg/ml	1:20
Normal saline 0.9%	9 mg/ml	1:1
Etomidate	2 mg/ml	1:100
Propofol	10 mg/ml	1:100
Succinylcholine	50 mg/ml	1:1 000
Vecuronium	4 mg/ml	1:1 000
Rocuronium	10 mg/ml	1:1 000
Mivacurium	2 mg/ml	1:10 000
Cis-atracurium	2 mg/ml	1:1 000
Atracurium	10 mg/ml	1:10 000
Sufentanil	0.005 mg/ml	1:100
Morphine HCl	10 mg/ml	1:100 000
Meperidine	50 mg/ml	1:10 000
Cefazolin	200 mg/ml	1:100

drugs used for intradermal skin testing are shown in Table 3. 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 if the weal has a diameter of 8 mm or more, surrounded by a flare (5, 7, 32). A skin prick test is considered positive if 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). Skin tests are relatively safe. The incidence of adverse reactions is less than 0.3%. Thus, resuscitation facilities have to be available (5).

Both tests have advantages and disadvantages. 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 the tests. Performing both tests improves the incidence of finding the responsible 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).

Not only the drugs used during the suspected anaphylactic reaction should be tested, but also all other available anaesthetics, 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 he reacts to at least one other NMBD is 66%, and the probability he reacts to more than 1 NMBD is 40%. The most frequent combinations are vecuronium and pancuronium, and succinylcholine and aminosteroid NMBDs (7, 11).

In patients with a history of anaphylactic reaction to a NMBD presenting for anaesthesia, 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). Whenever possible we should avoid NMBDs in these cases (41). If muscle relaxation is necessary, 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

Several other tests can be done: determination of specific IgE antibodies, the basophil activation test and the challenge test.

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, 41). 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, we can do this test. Performing both skin testing and RAST for specific IgE antibodies, increases the incidence of finding the responsible drug with 5% (41). 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, 41). 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 anaesthetics. First, the local anaesthetic is injected intradermally in increasing concentrations. If the intradermal skin test is negative with the undiluted concentration, the local anaesthetic 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 advice about future anaesthesia. To this letter the information of a future anaesthesia should be added. The patient should be encouraged to wear a medic alert bracelet (7, 30, 41).

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