

# ANAPHYLAXIS IN ANAESTHESIA AND CRITICAL CARE

**Stephanie SF Fischer, MB BCh, FCA (SA)**

*Department of Critical Care and Anaesthesia, Red Cross Children's Hospital, University of Cape Town, South Africa*

## ABSTRACT

Anaphylaxis during anaesthesia or in the intensive care unit may be an acute and dramatic adverse event. Even so, such reactions are frequently ascribed to clinical changes associated with the surgical procedure or the patients' underlying pathology sooner than being acknowledged as an adverse drug reaction. Subsequent determination of the responsible agent is complex and requires a multi-disciplinary approach.

## INTRODUCTION

Anaesthetists administer numerous drugs in rapid succession while providing general anaesthesia. Critical care physicians make use of similar pharmaceutical agents in the intensive care unit (ICU). Therefore these two groups of medical practitioners are most likely to encounter severe adverse drug reactions. Several authors have reviewed this topic in the recent literature.<sup>1-3</sup>

Adverse reactions comprise those that are dose dependent and related to the pharmacological properties of the drug, as well as reactions that are unrelated to the pharmacological properties and dose of the drug, known as anaphylactic reactions. The term anaphylaxis includes immune-mediated and non-immune-mediated allergic reactions (previously known as anaphylactoid reactions).<sup>1</sup> Immune-mediated anaphylaxis is a systemic, immediate hypersensitivity reaction resulting from IgE-mediated release of mediators from mast cells and basophils. These mediators are firstly granule-associated preformed mediators, followed by membrane-derived lipid mediators and then chemokines and cytokines.<sup>3-5</sup>

The exact aetiology of non-immune-mediated anaphylaxis is less transparent. The likely pathogenic mechanisms include idiosyncratic events, non-specific complement activation, activation of proteolytic systems such as the clotting cascade and direct histamine release.<sup>1</sup>

## INCIDENCE

Peri-anaesthetic anaphylaxis is becoming more common; yet the true incidence is poorly defined. Some countries such as France have established a national reporting system to delineate the problem more methodically. Still under-reporting is prevalent and estimated at greater than 30%. The probable overall frequency ranges between 1 out of every 3 500 to 20 000 general anaesthetic administrations.<sup>1,2</sup>

Correspondence: Dr S Fischer, Department of Critical Care and Anaesthesia, Red Cross Children's Hospital, Klipfontein Road, Rondebosch 7700. Tel 072-175-1159, e-mail: stephanie.fischer@uct.ac.za

Mortality rates for anaesthesia-related reactions have been quoted as between 3% and 6%, and even up to 10% in the UK. An additional 2% of patients suffer from residual brain damage.<sup>2,6</sup>

## AGENTS

Most common causative agents are muscle relaxants (60%) followed by latex, hypnotics, antibiotics, plasma substitutes and opioids. No anaphylactic reaction to inhaled anaesthetics has been published.<sup>7</sup>

### *Muscle relaxants*

Muscle relaxants are the most common agents causing anaphylaxis during anaesthesia, accounting for 60-70% of all reactions. Rocuronium and succinylcholine appear to be the most frequently incriminated agents.<sup>8</sup>

Most muscle relaxants can cause hypersensitivity reactions by both direct release of histamine from mast cells in addition to IgE-mediated mechanisms. Life-threatening reactions are typically IgE-mediated; the ammonium group common to all muscle relaxants is recognised and bound by IgE. Cross-reactivity is a problem with neuromuscular blocking agents. No less than 60-80% of patients allergic to one muscle relaxant may also react to another. Cross-reactivity extends across different classes of neuromuscular blocking agents and other classes of non-anaesthetic pharmaceuticals. Moreover previous exposure to these agents is not essential for sensitisation to occur. This is thought to be due to exposure to quaternary ammonium groups found in cosmetics, over-the-counter medications and cleaning products, and is borne out by the higher incidence of allergic reactions to muscle relaxants in women.

### *Latex*

Latex and natural rubber by-products are substances found in many surgical and non-surgical products in the hospital. Intra-operative latex anaphylaxis has been recognised as an important problem over the last 20 years. Latex allergy accounted for 10% of anaphylactic reactions during surgery in 1996 and this increased to 16% by 2000. Although figures have stabilised secondary to heightened awareness and widespread use of latex-free environments, latex remains the second most common cause of peri-operative anaphylaxis.<sup>1,8</sup>

Persons at risk for latex allergy include those with increased exposure to latex such as healthcare workers, children needing repeated catheterisation and multiple medical and surgical procedures, and those with a genetic predisposition, characteristically atopic individuals.<sup>9</sup>

The prevalence of latex sensitisation in medical staff working in the operating environment is as high as 12%. Though sensitisation does not always lead to an anaphylactic reaction, continued exposure to latex will increase the possibility of a reaction.<sup>10</sup>

Latex is not considered a medication and therefore often not considered in the differential diagnosis of anaphylaxis; this leads to incorrect diagnosis. Dis-

tinctive features of latex allergy include a history of generalised atopy or specific allergy to certain fruits, previous repeat exposure as well as a delayed reaction occurring 30-60 minutes into the procedure, in contrast to reactions secondary to anaesthetic drugs which usually occur within 10 minutes of the drug exposure.

### **Antibiotics**

Reactions to antibiotics have increased, possibly as a result of increased exposure to antibiotics in the community. Most commonly implicated antibiotics are beta-lactam antibiotics and vancomycin.<sup>1</sup> Together, penicillin and cephalosporins account for 70% of peri-operative anaphylactic reactions to antibiotics, most being IgE-mediated reactions.<sup>2</sup> Vancomycin may lead to life-threatening non-IgE-mediated anaphylaxis, thought to be due to direct histamine release as well as direct myocardial depression. These effects may be minimised by reducing the rate of administration of vancomycin.

### **Hypnotics**

Hypnotic agents of various classes are used peri-operatively for anaesthetic induction and in the ICU as sedative agents or anticonvulsant therapy.

Thiopental is a short-acting barbiturate. Reactions are uncommon nowadays reflecting the more frequent use of newer, non-barbiturate induction agents. Allergy testing includes skin testing and detection of specific IgE. Cross-reactivity with other barbiturates such as pentobarbitone, phenobarbitone, barbitone and methohexital may be present.

Propofol is an alkyl phenol. Specific IgE against the isopropyl groups of the molecule may occur although most adverse reactions to propofol seem to be non-immunological.<sup>1</sup> A concentration-dependent histamine release from lung mast cells may lead to bronchospasm. Diagnosis of allergy is with skin testing, specific IgE and histamine release tests.

Etomidate, an imidazole derivative and ketamine, a phenylcyclidine derivative, as well as midazolam, a short-acting imidazobenzodiazepine, are rarely implicated in allergic reactions.<sup>2</sup>

### **Opioids**

Opioid-induced anaphylaxis is atypical. Generalised reactions are usually inconsequential and occur from non-specific skin mast cell activation leading to pruritus, urticaria and mild hypotension. Reducing the rate of administration usually limits the severity of these reactions. Fentanyl is known not to cause direct histamine release. Immune-mediated reactions secondary to some opioids have been described in the literature.<sup>11</sup> Skin-prick testing has not been found to be useful for validating opioid allergy.

Placebo controlled challenges can be utilised to aid diagnosis.<sup>2</sup>

### **Plasma volume expanders**

Dextran, hydroxyethyl starch (HES) and gelatins may be used as high oncotic fluid replacement in theatre as well as the ICU.

Reactions to colloids make up 4% of all peri-operative anaphylactic reactions according to international studies.<sup>8,12</sup> Anaphylaxis from colloids may take place immediately or it may be delayed.

Both the mechanism and diagnostic testing in the case of hypersensitivity reactions to these agents have not been established.

### **Local anaesthetics**

Local anaesthetics are made up of two classes of drugs, the para-minobenzoic acid esters and the amides. Immunological reactions are rare and often adverse signs and symptoms are due to known side-effects and/or toxicity. Additives to local anaesthetics such as vasoconstricting agents and preservatives may themselves lead to undesirable and possibly allergic reactions.

### **Others**

Various other non-anaesthetic agents can induce anaphylaxis. Agents used during cardiothoracic surgery or in the cardiothoracic ICU such as aprotinine, protamine and heparin may lead to fatal reactions. Intravenous protamine, an agent used to reverse heparin and anti-coagulation, may cause allergic and non-allergic anaphylaxis. Protamine can cause significant histamine release resulting in hypotension and bronchospasm and also causes pulmonary hypertension. Aprotinin is used in cardiac surgery to control bleeding and to decrease transfusion rates. Multiple administrations may lead to hypersensitivity reactions.

Chlorhexidine is a commonly applied topical antiseptic solution and disinfectant. Severe life-threatening reactions have been associated with mucosal and parenteral exposure. Reactions to cutaneous applications peri-operatively are often missed and underestimated.

## **CLINICAL GUIDELINES**

The accent of clinical guidelines must be on recognition, investigation and prevention of peri-anaesthetic anaphylaxis.

### **Recognition**

Clinical recognition of anaphylaxis in the ICU and during anaesthesia is not straightforward. Induction of anaesthesia involves exposure to multiple drugs along with non-anaesthesia-related drugs and procedures performed at the same time. Respiratory and cardiovascular manifestations characteristic of allergic reactions are also common side-effects of anaesthesia or may be attributable to physiological changes secondary to positioning and surgical manipulation. In the critical care setting underlying haemodynamic and respiratory parameters are commonly deranged, and in turn deterioration of these parameters secondary to allergic reactions needs to be differentiated from exacerbation of the patient's underlying pathology. In addition the clinical syndrome associated with an anaphylactic reaction may well be very variable. Often the most severe reactions involve only one system. Ten per cent of reactions involve only cardiovascular collapse.<sup>6</sup> Furthermore it is not possible to differentiate immune-mediated reactions from non-immune-mediated reactions on clinical grounds alone. Nonetheless some studies identified an increase of both occurrence and severity of cardiovascular and pulmonary events secondary to immunologically mediated reactions versus predominantly cutaneous manifestations in chemically mediated reactions.<sup>8</sup>

### **Diagnostic investigations**

An elevated serum tryptase level supports the diagnosis of anaphylaxis, immune- or non-immune-mediated. On the other hand a negative tryptase result does not exclude anaphylaxis. The study by Mertes *et al.*<sup>9</sup> reports a significantly elevated tryptase level in 64% of immune-mediated reactions and in only 10.7% of non-immune-mediated reactions. They found tryptase lev-

els above 25 µg/l to have a positive predictive value of 92.6% and a negative predictive value of 54.6% for immune-mediated reactions. Higher levels are relatively specific for immune-mediated reactions as basophils possess minimal amounts of tryptase. Severe reactions are often associated with the highest levels. The tryptase level peaks at approximately 30 minutes and then gradually decreases. Its half-life is 2 hours. This gives clinicians a mechanism in the peri-operative period or in the critical care setting for verifying the occurrence of an anaphylactic reaction and allows for potential differentiation between allergic and non-allergic mechanisms. It is also important both medicolegally and for subsequent patient management.

An agent responsible for an adverse reaction can only be precisely identified in the case of immune-mediated anaphylaxis. Patients are often exposed to a large number of potential allergens during anaesthesia and surgery, as well as in the ICU. A Danish study<sup>13</sup> found the median number of potential allergens to which patients were exposed peri-operatively to be between 7 and 9 different agents.

Attempts at identifying the causative agent retrospectively by both *in vitro* blood tests as well as intradermal and skin-prick testing are fraught with controversies.

None of the available diagnostic tests demonstrate absolute accuracy. The lack of internationally accepted guidelines on skin testing may account for the apparently different incidences of allergy to muscle relaxants among countries. Recommendations as to the optimal drug concentration for skin testing with muscle relaxants are conflicting.<sup>8,14,15</sup> Dhonneur *et al.*<sup>14</sup> described positive skin reactions with undiluted muscle relaxant (rocuronium and vecuronium) solutions in healthy, non-sensitised individuals and questioned assigning causality for allergic reactions to muscle relaxants based on positive skin tests. Others observed dissimilar results to Dhonneur.<sup>16</sup>

Nevertheless, at present skin testing remains the gold standard for detection of IgE-dependent allergies. Tests should be done after a delay of at least 6 weeks. If carried out earlier, there is an association with an increased risk of false-negative results because of refractoriness of the effector cell or temporary depletion of IgE antibodies. A detailed history and chronological account of the events around the time of the reaction, as well as the results of blood tests taken at the time, are considered necessary prior to performing skin testing. All drugs listed in the anaesthesia record except for inhalational agents, as well as latex and other chemicals administered, must be included in the testing.

Serology involves the quantitative measurement of serum-specific IgE antibodies to the implicated agent. Assays for IgE antibodies to muscle relaxants, thiopentone and latex are available. The result of these assays can be helpful in the interpretation of negative skin results in the midst of highly suggestive clinical signs. Flow cytometric analysis and quantification of *in vitro* activated basophils can add to the diagnosis of anaphylaxis from anaesthetic agents.<sup>17</sup> Progressive challenge testing is limited to local anaesthetics and latex, and is only done after skin tests are negative.

### Prevention

The key elements of prevention include a careful medical history that focuses on previous adverse events. Atopic patients have an increased risk for latex reactions. However a history of generalised allergy is not associated with an increased risk of anaphylaxis during anaesthesia. Conversely, cross-reactivity between

anaesthetic agents may be as high as 80% and therefore a patient history of allergy to anaesthetics is reason for concern, further evaluation and specific testing. As in other forms of allergic reactions, the prevalence of sensitisation is higher than the incidence of reactions.<sup>9,18</sup> Hence pre-anaesthetic screening is not indicated for allergy to muscle relaxants.

It is also not currently recommended to screen patients for latex allergy before a surgical procedure in the absence of a suggestive history. Doing so may significantly overestimate the incidence of latex sensitisation.<sup>10</sup> Instead an active policy to identify at-risk patients at the time of the pre-anaesthetic visit should be in place.

Pharmacological prophylaxis with antihistamines and corticosteroids may possibly be valuable for the prevention of non-immune-mediated reactions. These medications however do not produce any changes in the sensitised mast cells and basophils. Therefore, while diminishing the early immune response, they may blunt the early signs of anaphylaxis and lead to a very severe response, such as cardiovascular collapse, as the only presenting sign.

### CONCLUSION

Anaphylaxis during anaesthesia or in the critical care setting may be potentially severe and associated with adverse outcomes. Prompt recognition and immediate treatment, the 'anaphylaxis drill', must be part of the attending physician's repertoire. Every patient presenting with a hypersensitivity reaction during anaesthesia must undergo immediate as well as secondary investigations. It is the responsibility of the attending physician, the anaesthetist or intensivist, to initiate the investigation.

False-positive results may merely cause inconvenience and unnecessary avoidance of a safe drug, whereas false-negative results may be extremely dangerous and severely undermine correct secondary prevention. These relative complexities of allergy investigation emphasise the need for specialised alleryo-anaesthesia centres to provide expert advice to anaesthetists and allergists. Ideally diagnosis of anaphylaxis peri-operatively and in the ICU should rest upon different confirmatory tests rather than on a single one.<sup>2</sup> A combination of specialised investigations should include: tryptase measurements, skin-prick testing, intradermal testing and high performance specific IgE immunoassays.<sup>2</sup> Advice concerning matters of future anaesthetic technique and indications need to come from the anaesthetist.<sup>7</sup>

### Declaration of conflict of interest

The author declares no conflict of interest.

### REFERENCES

1. Chacko T, Ledford D. Peri-anesthetic anaphylaxis. *Immunol Allergy Clin N Am* 2007; **27**: 213-230.
2. Ebo D, Fisher M, Hagendorens M, *et al.* Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* 2007; **62**: 471-487.
3. Ogawa Y, Andrew G. Mediators of anaphylaxis. *Immunol Allergy Clin N Am* 2007; **27**: 249-260.
4. Kay A, Rosen F. Allergy and allergic diseases. *N Engl J Med* 2001; **344**: 30-37.
5. Kay A. Allergy and allergic diseases. *N Engl J Med* 2001; **344**: 109-113.
6. Axon A, Hunter J. Anaphylaxis and anaesthesia – all clear now? *BJA* 2004; **93**: 501-504.
7. Mertes P, Laxenaire M, Lienhart A, *et al.* Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. *J Invest Allergol Clin Immunol* 2005; **15**: 91-101.

8. Mertes P, Laxenaire M, Alla F, *et al.* Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999-2000. *Anesthesiology* 2003; **99**: 536-545.
9. Lieberman P. Anaphylactic reactions during surgical and medical procedures. *J Allergy Clin Immunol* 2002; **110**: S64-69.
10. Hepner D, Castells M. Latex allergy: an update. *Anesth Analg* 2003; **96**: 1219-1229.
11. Cummings K, Arnaut K. Case report: fentanyl-associated intraoperative anaphylaxis with pulmonary edema. *Can J Anesth* 2007; **54**: 301-306.
12. Harboe T, Guttormsen A, Irgens A, *et al.* Anaphylaxis during anesthesia in Norway. *Anesthesiology* 2005; **102**: 897-903.
13. Kroigaard M, Garvey L, Menne T, *et al.* Allergic reactions in anaesthesia: are suspected causes confirmed on subsequent testing? *BJA* 2005; **95**: 468-471.
14. 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**: 986-989.
15. Levy J. Reactions to neuromuscular blocking drugs: are we making the correct diagnosis? *Anesth Analg* 2004; **98**: 881-882.
16. Tamayo E, Rodriguez-Ceron G, Gomez-Herreras J, *et al.* Prick-test evaluation to anaesthetics in patients attending a general allergy clinic. *Eur J Anaesthesiol* 2006; **23**: 1-6.
17. Boumiza R, Monneret G, Forissier M, *et al.* Marked improvement of the basophil activation test by detecting CD203c instead of CD63. *Clin Exp Allergy* 2003; **33**: 259-265.
18. Porri F, Lemiere C, Birnbaum J, *et al.* Prevalence of muscle relaxant sensitivity in a general population: implications for a preoperative screening. *Clin Exp Allergy*. 1999; **29**: 72-75.

## NEWS

### ***Third Jack Pepys Workshop on Asthma in the Workplace and research award for South African researcher***

The third Jack Pepys Workshop on Asthma in the Workplace was held on 18 and 19 May 2007 in the amphitheatre of the Pavillon Jean-Coutu on the campus of the Université de Montréal, Canada. The two-day workshop was organised by the Asthma in the Workplace Center in conjunction with the Institut de recherche Robert-Sauvé en santé et sécurité du travail (IRRSST) and the Commission de la santé et sécurité du travail (CSST) (both in Quebec) and the Workplace Safety and Insurance Board (WSIB) in Ontario. Prof Mohamed Jeebhay from the University of Cape Town was invited to attend this workshop, which focused on review of scientific advances since the previous workshop held in Toronto in 2004 with a view to generating additional scientific hypotheses in this area. The workshop brought together international experts in occupational asthma for two days of lively discussions on the latest discoveries and controversies. His contributions were specifically in the deliberations around occupational asthma in developing countries as well as the session on public health, surveillance and prevention

issues with a special focus on exposure reduction. Prof Jeebhay together with colleagues Catherine Lemière, Samah Chiry, Jean-Luc Malo from Canada and Olivier Vandenplas from Belgium, was also recently awarded one of eight international research scholarships awarded by the Centre for Asthma in The Workplace (Canada) for their studies on exhaled nitric oxide in the investigation of occupational asthma.

### ***South African recipient of WAO/Nycomed Fellowship announced***

Congratulations to Dr T Moodley of Pretoria Academic Hospital who has been awarded the WAO/Nycomed Fellowship research award.

#### **Clinical Allergy Images**

Do you have an interesting clinical image to share with our readers? Please send your images and a brief outline of the case to the Clinical Allergy Images Section Editor, Dr George du Toit, [georgedutoit@gmail.com](mailto:georgedutoit@gmail.com)