ALLERGIC REACTIONS AND ANAPHYLAXIS DURING ANAESTHESIA

JM Dippenaar | MBChB, DA(SA), MMed (Anes)¹
S Naidoo | MBChB, MMed (Anes)²

1. Principal Specialist Anaesthesiology, Department of Maxillo Facial Oral Surgery, Oral and Dental Hospital, University of Pretoria
2. Specialist Anaesthesiology, Department of Anaesthesiology and Intensive Care, Kalafong Hospital, University of Pretoria
Email | tinus.dippenaar@up.ac.za

ABSTRACT

Although allergic reactions during anaesthesia are rare, it may have potentially life threatening consequences when anaphylaxis develops. Should a patient have a possible reaction under anaesthesia, it is important to identify an offending agent to prevent re-exposure during subsequent procedures. This review aims to identify common causes of anaphylaxis during anaesthesia, how to deal with the emergency, and how to follow up the at-risk patient.

INTRODUCTION

Anaphylaxis during anaesthesia is a rare phenomenon, but may have life threatening consequences when encountered and if not managed correctly. In the context of allergic reactions and anaphylaxis, anaesthesia represents a uniquely hazardous situation for a number of reasons. Firstly, the anaesthetist is alerted to the crisis only when it is severe enough to cause rapid cardiovascular and respiratory compromise (Table I), leaving little time to manage the crisis. Early signs and mild symptoms remain virtually unrecognised as, or when patients are unconscious and covered with surgical drapes, preventing observation of the initial skin manifestations. Secondly, the severity of the reaction may be underestimated by the anaesthetist. The cardiovascular deterioration may initially be masked by a light plane of general anaesthesia (or an extensive regional block). Conversely, hypotension and difficulty in ventilation may have other more common causes that need to be excluded first. Thirdly, multiple drugs are administered over a short period of time. Some are known histamine releasers, while others are recognised for their allergenic potential. To identify the offending substance during the crisis is mere guesswork. Fourthly, allergenic agents are not limited to intravenous drugs or fluids, but include other substances used in the operating room such as skin disinfectants, latex gloves and catheters. Skin or mucosal application leads to delayed onset of reaction, often presenting 15-30 minutes into a procedure.

The worldwide reported rate of allergic reactions during anaesthesia is difficult to estimate, with quoted incidences of 1:3500⁶ (Canada), 1:6000² (Norway), 1:10000 to 1:20000⁷ (Australia) and 1:34000⁸ (single centre, USA), with anaphylaxis having a mortality rate of 3.5%⁹ to 10%¹⁰ (again, depending on the origin of the data). Accurate figures remain unknown as underreporting is frequent. Allergies to every drug used in anaesthesia (except the volatiles) have been documented, with muscle relaxants and antibiotics alternating as leading causes.

PATHOPHYSIOLOGY

Anaphylaxis is an immediate immunologically mediated severe allergic reaction to an administered substance. Classified as a type I hypersensitivity reaction (according to Gell and Coombs), it is now recognised that the reaction may be IgE-mediated or non IgE-mediated (in lieu of anaphylactoid). Initial sensitisation occurs when the T lymphocytes in susceptible patients are presented with an allergen, and in response produce IgE antibodies. The IgE antibodies bind to high affinity FεRI receptors on mast cells and basophils, and to low affinity FεRII receptors of leucocytes, platelets and eosinphils. Re-exposure to the same allergen results in multivalent cross-linking of the IgE antibodies bound to the high affinity receptors, activating intracellular transduction cascades with release of preformed mediators (histamine, tryptase, chymase, and heparin) from mast cells and basophils. This induces the release of pro-inflammatory phospholipid derived mediators (prostaglandin D₂, leukotrienes, platelet activating factor (PAF), thromboxane A₂) which in turn cause the release of chemokines and cytokines, with recruitment of inflammatory cells. A very small amount of antigen is required for this mechanism.

Non IgE-mediated immunologic type I reactions are clinically indistinguishable from the IgE-mediated response, and can occur on first exposure to an allergen. IgG-mediated reactions are less frequent and less serious than IgE-mediated reactions.
be triggered directly (with physical factors such as cold or heat, morphine and vancomycin), or may be released in response to bradykinin or complement activation. \(^{17}\) IgG binding to certain antigens may produce a similar effect. \(^{18}\) IgG-antigen complexes bind to F_{c}RIII receptors on macrophages and/or basophils\(^{19}\) mediating the release of PAF (but not histamine). PAF mediates smooth muscle relaxation and enhances vascular permeability. This mechanism requires a much larger IgG-antibody interaction than the IgE-mediated response. \(^{20}\) IgG also functions as a negative feedback mechanism on the IgE-mediated pathway, inhibiting IgE-mediated histamine release.

PREVENTION AND DIAGNOSIS
A careful and specific history of adverse or allergic drug reactions and subsequent avoidance of these drugs are the safest way to prevent peri-operative anaphylaxis. A history of food allergy, asthma, atopic patients (elevated/increased IgE levels); patients that have had multiple surgical procedures and healthcare workers exhibit increased risk for reacting to latex and radio contrast media. Female patients are three times more prone to allergies to latex and neuromuscular blocking agents (NMBA) than males. \(^{21}\) Many smokers exhibit sensitivity to antibiotics by virtue of repeated exposure to antibiotics for respiratory tract infections. Asthma therapy and \(\beta\) blocker use may lead to the development of severe anaphylaxis that is refractory to the conventional treatment options. Patients on \(\beta\) blocker therapy, that demonstrate resistance to the effects of adrenaline, mandates glucagon administration (1-5 mg) as part of the resuscitation effort. \(^{22}\) Premedication with histamine (H) 1 or 2 receptor antagonists or glucocorticoids are not advantageous, as it rarely prevents the reaction and may blunt the initial onset and delay diagnosis. \(^{23}\) These drugs should be reserved for early treatment of the anaphylactic event.

The initial diagnosis of anaphylaxis relies on clinical grounds (Table I), and should be followed by retrospective confirmation via skin testing and serology.

The increase in serum tryptase is considered a fairly reliable indicator of mast cell degranulation, not of an anaphylactic reaction as such. Levels reach diagnostic levels within 30 minutes of the onset of a reaction, and as enzyme half-life is 2 hours, early collection of serum for testing is necessary. Tryptase levels may not be elevated even when a reaction is confirmed by IgE antibody titres, or in the absence of hypotension. \(^{24}\) Conversely, drugs that cause direct mast cell degranulation will increase tryptase levels.

SPECIFIC DRUGS
NEURO MUSCULAR BLOCKING AGENTS (NMBAs)
The muscle relaxants as a group cause about 60% of immediate hypersensitivity reactions. The quaternary ammonium structure is the main contributing factor in development of allergic reactions. \(^{21}\)

Although uneventful first exposure to an NMBA may cause sensitisation with type I reaction at next exposure, most reactions to NMBA’s occurs without previous exposure to the specific agent. Common household chemicals (shampoo, detergents, toothpaste) and even opioids share the quaternary ammonium group in their respective core molecular structure responsible for cross-sensitisation of the immune system. In Norway, where pholocodeine (opiod cough suppressant) is available as an over-the-counter medicine, there is an unusually high incidence of allergies to NMBA’s. \(^{27}\)

Most cases of anaphylaxis are described with the use of succinylcholine. \(^{28}\) The inherent mobility of the molecular structure favours binding to IgE antibodies with subsequent reaction. Rocuronium has a slightly less mobile structure, but may bind to IgE in similar fashion. \(^{29}\) Anecdotal evidence suggests that sugammadex, an alternative reversal agent for amino steroid non-depolarising NMBA’s may terminate the anaphylactic reaction as it chelates and removes the offending rocuronium molecules. \(^{30}\)

Benzyisoquinoliniums such as mivacurium and atracurium causes direct mast cell degranulation, when injected fast, causing a typical wheal and flare reaction. This may extend systemically as well, so it is prudent to avoid these drugs in the atopic population. \(^{31}\) Cisatracurium, an isomer of atracurium, is not associated with histamine release, even though it shares the same benzyisoquinolinium structure. \(^{32}\)

Routine skin testing with muscle relaxants is not recommended as the positive predictive value is so small. If the offending agent is definitely a muscle relaxant, testing with specific agents will yield a high predictive value. \(^{33}\) Drugs like atracurium and mivacurium are well known to increase local and systemic histamine levels, often without IgE response. \(^{34}\) Because of cross-reactivity, morphine radio immune assay (RIA) is highly sensitive for detection of IgE antibodies to muscle relaxants. \(^{35}\)

ANTIBIOTICS
Penicillin is responsible for about 70% of anaphylactic reactions in the general population. \(^{36}\) Yet, only 10-20% of patients reporting penicillin allergy in the peri-operative period have actual documented proof of such allergy. \(^{37}\) Many texts still quote an 8-10% cross reactivity for 1st generation cephalosporins in penicillin allergy, possibly because they share a beta-lactam ring structure. Current recommendation is that 2nd and 3rd generation cephalosporins may be cautiously administered to individuals with penicillin allergy, but not anaphylaxis, due to penicillin. \(^{38}\) Vancomycin, when administered over a short period of time is known to cause generalised histamine release – “Red Man Syndrome”. \(^{39}\) Anaphylaxis to other antibiotics is rare in anaesthesia.

LATEX
Latex is a natural rubber which is derived from the sap of Hevea brasiliensis. It causes about 20% of all anaphylac-
tic reactions in the peri-operative period.\textsuperscript{40} The incidence seems to be decreasing as awareness and avoidance of latex during the peri-operative period becomes more frequent.\textsuperscript{2} High risk groups include atopic patients, patients with food and fruit allergies (banana, mango, kiwi, avocado, chestnuts), children repeatedly undergoing surgical procedures from early ages (specifically spina bifida),\textsuperscript{41} health care workers,\textsuperscript{42} and patients with severe contact dermatitis of the hands.\textsuperscript{43} Renewed interest in the association of latex during the peri-operative period becomes more frequent.\textsuperscript{44} However, the incidence of latex allergy seems to be decreasing as awareness and avoidance becomes more widespread.\textsuperscript{45}

During anaesthesia there are several points of possible contact which can trigger a reaction including use of gloves by the healthcare provider, intravenous injection of drugs, even insertion of urine catheters and endotracheal tubes. Avoidance is the only effective treatment option at the moment, although desensitisation by repeated contact exposure of an allergic individual to latex, has been reported.\textsuperscript{46}

**LOCAL ANAESTHETICS**

Anaphylaxis due to local anaesthetics (LA) is exceedingly rare.\textsuperscript{47} Esters such as tetracaine and benzocaine are metabolised to para-amino-benzoic acid (PABA) which can provoke a type I IgE-mediated reaction. The preservatives methylparaben and metabisulphite, is the second most likely culprit in LA anaphylaxis.\textsuperscript{48} It is therefore imperative that a preservative free local anaesthetic is used when a patient is subjected to skin or challenge testing. There is no cross sensitisation between ester and amide groups of LA drugs. Systemic toxicity should always be considered when a patient presents with cardio-respiratory collapse after LA injection.

**OPIOIDS**

True anaphylaxis has been reported with every opioid drug, but the incidence is extremely low. The tertiary amine structure of morphine, codeine and meperidine (Pethidine\textsuperscript{49}) predisposes to mast cell degranulation with histamine release, with meperidine being the most common offender.\textsuperscript{40} This may confound the results of skin testing when searching for an offending opioid. Cross reactivity exists between opioids of the same group, except in the phenylpiperidine group (fentanyl sufentanil, alfentanil, remifentanil).\textsuperscript{28}

**INDUCTION AGENTS**

Propofol is responsible for 1.2% to 2% of all peri-operative anaphylactic reactions.\textsuperscript{49} Current formulation in an emulsion of soy oil, egg albumin and glycerol (Intalipid\textsuperscript{50}) may suggest cautious use in patients with egg or soy allergy, but there is no evidence to show increased risk of anaphylaxis in this population.\textsuperscript{50} Isopropyl groups present in skin care products may induce IgE sensitisation with subsequent cross reaction with the isopropyl groups of the propofol molecule.\textsuperscript{51}

The incidence of thiopentone allergy is 1:30000, but since it is rarely used these days, reports of reactions to it are very rare too.\textsuperscript{52} Ketamine allergy is extremely rare\textsuperscript{40}, and etomidate is deemed the “most immunologically safe drug” in anaesthesia.\textsuperscript{53}

Anaphylaxis to benzodiazepines (BZ) is extremely rare. Diazepam is dissolved in a propylene glycol base, making it more likely to cause anaphylaxis than midazolam.\textsuperscript{40} The desmethyldiazepam metabolite is responsible for cross reactivity with other BZ’s. Midazolam has no metabolites, and is considered the immunologically safest BZ.\textsuperscript{54}

**VOLATILE AGENTS**

There is not a single report of any anaphylactic reaction to any of the volatile agents. The rare fulminating form of hepatitis associated with halothane use is thought to have an immune component but is unrelated to anaphylaxis.\textsuperscript{55}

**OTHER POTENTIAL PERI-OPERATIVE ALLERGENS**

Topical antiseptics such as povidone-iodine (betadine) and...
The reactivity between the different colloids does not exist. Colloids account for 2.5% of all anaphylactic reactions intra-operatively. Colloids are plasma volume expanders used to restore intravascular volume during surgery and trauma. The administration of adrenalin (epinephrine) is the cornerstone of treatment. Endotracheal intubation with delivery of 100% oxygen via positive pressure ventilation is needed to compensate for increased oxygen consumption. Circulatory support includes administration of large volumes of intravenous fluids (2-4l of crystalloids) to counteract the loss of intravascular volume due to capillary leakage, and administration of adrenalin (epinephrine – α and β agonist). The α-effect counteracts hypotension by increased cardiac contractility and vasoconstriction, while the β-effect induces bronchodilation. Hypotension necessitates boluses of 5-10 μg (0.2 μg/kg) as needed, but CVS collapse requires 0.5-1 mg (0.2 mg/kg) boluses.

To counter the effects of released mediators, it is necessary to also administer H1 (diphenhydramine) and H2 (cimetidine, ranitidine) receptor antagonists. Persistent bronchospasm will necessitate the use of pure β2 agonists (salbutamol). Glucocorticoids have mast cell stabilising properties, are anti-inflammatory and therefore will prevent recurrence and minimise airway swelling. Hydrocortisone is the preferred corticosteroid because of its fast onset of action.

Once the patient is stable the airway may be extubated. The patient will need close observation in the ward for 24 hours. Airway swelling, persistent or recurrent bronchospasm and haemodynamic instability will delay extubation and admission to an intensive care unit will be necessary.

**SUMMARY**

Although most drugs used in the perioperative period can cause anaphylaxis, it is fortunately a rare event. To identify the offending agent during the procedure is difficult, and patients are not always referred for post-operative testing. Skin testing may confirm the identity of the offending agent in a minority of patients only. Muscle relaxants, latex and chlorhexidine have rarely been reported as allergens. A history of sensitivity to iodine or reaction or positive skin testing precludes the use of these substances in relevant patients.

Iodated contrast media contain free iodine fractions that may stimulate a reaction. Non-ionic media are prone to cause grade 1 (cutaneous manifestations) reactions, and pre-treatment with antihistamines and corticosteroids are effective in preventing these reactions. The larger hyperosmolar, ionic media may cause a non IgE-mediated reaction, and steroid pre-treatment does not prevent it.

Colloids are plasma volume expanders used to restore intravascular volume during surgery and trauma. Colloids account for 2.5% of all anaphylactic reactions intra-operatively. The incidence of allergic reactions is estimated to be 0.06% for the hydroxyl-ethyl starches, 0.1% for albumin, 0.26% for dextrans and 0.34% for gelatins. Cross reactivity between the different colloids does not exist.

**MANAGEMENT**

Once anaphylaxis is recognised, management consists of three distinct actions: i) withdrawal of the offending substance, ii) interrupting the effects of the preformed mediators released in response to antigen presentation, and iii) prevention of further mediator release. See Table II for a summary of management.

<table>
<thead>
<tr>
<th>IMMEDIATE MANAGEMENT</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary treatment</td>
<td></td>
</tr>
<tr>
<td>Stop administration</td>
<td></td>
</tr>
<tr>
<td>Call for help, inform surgeon</td>
<td></td>
</tr>
<tr>
<td>Trendeleberg position</td>
<td></td>
</tr>
<tr>
<td>Airway management – oxygen</td>
<td></td>
</tr>
<tr>
<td>Adrenalin</td>
<td>FIO2 = 1</td>
</tr>
<tr>
<td>Dilute to 100 μg/ml</td>
<td></td>
</tr>
<tr>
<td>Titrate to effect</td>
<td></td>
</tr>
<tr>
<td>Infusion (if large dose needed)</td>
<td></td>
</tr>
<tr>
<td>Fluid Therapy</td>
<td></td>
</tr>
<tr>
<td>Crystalloid or colloid</td>
<td></td>
</tr>
<tr>
<td>Secondary treatment</td>
<td></td>
</tr>
<tr>
<td>Antihistamine</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>B2 agonists nebulisation</td>
<td></td>
</tr>
</tbody>
</table>

Once anaesthesia relies mainly on intravenous drug administration, withdrawal of the offending agent is near impossible. Immediate institution of basic life support measures (airway, breathing, circulation) and the early administration of adrenalin (epinephrine) is the cornerstone of treatment. Endotracheal intubation with delivery of 100% oxygen via positive pressure ventilation is needed to compensate for increased oxygen consumption. Circulatory support includes administration of large volumes of intravenous fluids (2-4l of crystalloids) to counteract the loss of intravascular volume due to capillary leakage, and administration of adrenalin (epinephrine – α and β agonist). The α-effect counteracts hypotension by increased cardiac contractility and vasoconstriction, while the β-effect induces bronchodilation. Hypotension necessitates boluses of 5-10 μg (0.2 μg/kg) as needed, but CVS collapse requires 0.5-1 mg (0.2 mg/kg) boluses.

To counter the effects of released mediators, it is necessary to also administer H1 (diphenhydramine) and H2 (cimetidine, ranitidine) receptor antagonists. Persistent bronchospasm will necessitate the use of pure β2 agonists (salbutamol). Glucocorticoids have mast cell stabilising properties, are anti-inflammatory and therefore will prevent recurrence and minimise airway swelling. Hydrocortisone is the preferred corticosteroid because of its fast onset of action.

Once the patient is stable the airway may be extubated. The patient will need close observation in the ward for 24 hours. Airway swelling, persistent or recurrent bronchospasm and haemodynamic instability will delay extubation and admission to an intensive care unit will be necessary.

**SUMMARY**

Although most drugs used in the perioperative period can cause anaphylaxis, it is fortunately a rare event. To identify the offending agent during the procedure is difficult, and patients are not always referred for post-operative testing. Skin testing may confirm the identity of the offending agent in a minority of patients only. Muscle relaxants, latex and antibiotics are the most common anaesthetic allergens, and prevention is the most important component to decrease the risk. Post-operative referral to an allergist for identification of the causative allergen is important to prevent future incidents of anaphylaxis.

**REFERENCES**
