ALERTING ANAESTHETISTS TO THE POTENTIAL FOR ANAPHYLAXIS DURING ANAESTHESIA

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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 1:3500 (Canada), 1:6000 (Norway), 1:10000 to 1:20000 (Australia) and 1:34000 (single centre, USA), with anaphylaxis having a mortality rate of 3.5% to 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 anaphylatoid). 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 FεR1 receptors on mast cells and basophils, and to low affinity FεR2 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.\textsuperscript{17} IgG binding to certain antigens may produce a similar effect.\textsuperscript{18} IgG-antigen complexes bind to F\textsubscript{2/4}RIII receptors on macrophages and/or basophils\textsuperscript{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.\textsuperscript{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 (NMBAs) than males.\textsuperscript{21} Many smokers exhibit sensitivity to antibiotics by virtue of repeated exposure to antibiotics for respiratory tract infections. Asthma therapy and β blocker use may lead to the development of severe anaphylaxis that is refractory to the conventional treatment options. Patients on β blocker therapy, that demonstrate resistance to the effects of adrenaline, mandates glucagon administration (1-5 mg) as part of the resuscitation effort.\textsuperscript{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.\textsuperscript{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.\textsuperscript{26} 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.\textsuperscript{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 (opoid cough suppressant) is available as an over-the-counter medicine, there is an unusually high incidence of allergies to NMBa’s.\textsuperscript{27}

Most cases of anaphylaxis are described with the use of succinylcholine.\textsuperscript{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.\textsuperscript{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 succinylcholine molecules.\textsuperscript{30}

Benzylisoquinoliniums 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.\textsuperscript{31} Cisatracurium, an isomer of atracurium, is not associated with histamine release, even though it shares the same benzylisoquinolinium structure.\textsuperscript{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.\textsuperscript{33} Drugs like atracurium and mivacurium are well known to increase local and systemic histamine levels, often without IgE response.\textsuperscript{34} Because of cross-reactivity, morphine radio immune assay (RIA) is highly sensitive for detection of IgE antibodies to muscle relaxants.\textsuperscript{35}

**ANTIBIOTICS**

Penicillin is responsible for about 70% of anaphylactic reaction in the general population.\textsuperscript{36} Yet, only 10-20% of patients reporting penicillin allergy in the peri-operative period have actual documented proof of such allergy.\textsuperscript{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.\textsuperscript{38} Vancomycin, when administered over a short period of time is known to cause generalised histamine release – “Red Man Syndrome”.\textsuperscript{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-
Anaphylaxis due to local anaesthetics (LA) is exceedingly rare. Anaphylaxis due to contact exposure of an allergic individual to latex, has been at the moment, although desensitisation by repeated 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. 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) predisposes to mast cell degranulation with histamine release, with meperidine being the most common offender. 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).

INDUCTION AGENTS
Propofol is responsible for 1.2% to 2% of all peri-operative anaphylactic reactions. Current formulation in an emulsion of soy oil, egg albumin and glycerol (Intalipid®) 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. Isopropyl groups present in skin care products, latex and spina bifida has surfaced in recent literature.

VOLATILE AGENTS
There is not a single report of any anaphylactic reaction to any of the volatile agents. The rare fulminant form of hepatitis associated with halothane use is thought to have an immune component but is unrelated to anaphylaxis.

OTHER POTENTIAL PERI-OPERATIVE ALLERGENS
Topical antiseptics such as povidone-iodine (betadine) and other potential peri-operative allergens.
chlorhexidine have rarely been reported as allergens.56,57 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.58 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.59 The larger hyperosmolar, ionic media may cause a non IgE-mediated reaction, and steroid pre-treatment does not prevent it.60

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.2 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.61 Titrate to effect

<table>
<thead>
<tr>
<th>IMMEDIATE MANAGEMENT</th>
<th>DOSAGE</th>
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<tbody>
<tr>
<td>Primary treatment</td>
<td></td>
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<tr>
<td>Stop administration of substance</td>
<td></td>
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<tr>
<td>Call for help, inform surgeon</td>
<td></td>
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<tr>
<td>Trendeleberg position</td>
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<tr>
<td>Airway management – oxygen</td>
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<tr>
<td>Adrenalin</td>
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<tr>
<td>Dilute to 100 μg/ml</td>
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<tr>
<td>Titrate to effect</td>
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<tr>
<td>Infusion (if large dose needed)</td>
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<tr>
<td>Fluid Therapy</td>
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<tr>
<td>Crystalloid or colloid</td>
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<tr>
<td>Secondary treatment</td>
<td></td>
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<tr>
<td>Antihistamine</td>
<td></td>
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<tr>
<td>H1 antagonists: promethazine</td>
<td></td>
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<tr>
<td>0.3 - 1 mg/kg</td>
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<tr>
<td>H2 antagonists: ranitidine</td>
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<td>0.5 - 1 mg/kg</td>
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<tr>
<td>Corticosteroids</td>
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<tr>
<td>B2 agonists nebulisation</td>
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</tr>
<tr>
<td>Hydrocortisone 50mg/kg</td>
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<tr>
<td>Salbutamol 5-10 μg</td>
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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.61

Once the patient is stable the airway may be extubated. The patient will need close observation in the ward for 24 hours.26 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**


