

EDITORIAL**Anaphylaxis and anaesthesia****Elizabeth Armitage-Chan**

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Most of the drugs administered during the anaesthetic period have the potential to cause adverse reactions. As anaesthetists, there is therefore a need to be familiar with both the expected and rarer responses to drugs. Although rarely encountered, almost all agents have the potential of causing dramatic and possibly fatal anaphylactic-type reactions. Such reactions are linked by a common involvement of the release of histamine, however there the similarity ends and there is much variability in the pathogenesis, predictability, magnitude and severity of the responses.

Drugs such as meperidine, morphine and protamine, when administered intravenously, produce a predictable release of histamine and significant blood pressure decrease in almost all patients. Meperidine-induced histamine release in dogs and cats, and the association between this and the clinical signs of anaphylaxis seen following its administration, was noted as early as 1952 (Schachter 1952). This reaction is presumed to occur via a direct, pharmacological, drug-receptor interaction, which is independent of the immune system. Many other drugs are also known 'histamine-liberators', but the magnitude of histamine release, and hence the clinical manifestation of a reaction, varies between each. The speed of administration is also a factor and if these drugs are given carefully in dilute solutions they are less likely to elicit a noticeable response even though histamine may be measurably increased (Guedes et al. 2006).

In contrast to these pharmacological histamine-releasing drugs, the responses to which are reasonably predictable, almost any agent may cause an acute immunological hypersensitivity reaction, the dramatic and sometimes fatal systemic response of which is also primarily histamine-mediated. Such events are rare and unpredictable - vast numbers of patients will receive the same drug without it eliciting any harmful response. There are common culprits for causing these reactions, including iodinated contrast agents, antibiotics, latex, neuro-

muscular blocking agents (particularly rocuronium and succinylcholine) and colloid solutions (Mertes & Laxenaire 2004), however isolated case reports of anaphylaxis to many other agents can be found.

Understanding the underlying pathophysiology of these reactions is complex, and a number of questions arise. Is this reaction best described as allergic, anaphylactic or anaphylactoid? If a patient suffers a profound reaction to a drug, will the same (or worse) response be seen if the patient requires the same, or a structurally related agent in the future? Are patients with allergic airway, intestinal or skin disease more likely to suffer drug reactions, and if a high-risk patient is identified, is there any benefit to pretreatment with antihistamines or glucocorticoids? These questions not only present a challenge to our understanding of the background pharmacology and physiology but are also highly relevant to daily clinical management.

Two articles in this issue approach this problem from different angles. In one, reactions of varying severity are described in three dogs receiving gadolinium contrast agent (Girard & Leece, 2010). However in the other, Mair et al. (2010) fail to detect a cardiovascular response in any of 50 dogs studied during gadolinium injection. This highlights some of the problems associated with studying adverse drug reactions – while it is not possible to predictably recreate a reaction in a study population, it is no less dramatic or problematic when experienced.

Two review articles, both published in 2009 from the journals *Anesthesiology* and *Anaesthesia*, describe various aspects of anaphylactic reactions occurring during anaesthesia in people (Dewachter et al. 2009, Harper et al. 2009). Much discussion in these and earlier reviews concerns the differences between immune and non-immune mediated reactions. The classical allergic reaction, which is often of minimal severity (or asymptomatic) when the allergen is first encountered, but which may result in cardiovascular collapse and bronchoconstriction

at second and subsequent exposures, involves production of immunoglobulin E (IgE) in response to drug exposure. IgE binds high-affinity FcεR1 receptors on mast cell and basophil membranes. On re-exposure, binding of drug antigen to these receptors results in formation of cross linkages, receptor activation and an intracellular signal transduction cascade leading to release of histamine, production of inflammatory leukotrienes and prostaglandins, and nitric oxide synthase upregulation. Clinical manifestations are truly systemic, involving the skin (oedema, redness, pruritus), gastrointestinal tract (vomiting, diarrhoea), cardiovascular system (vasodilation, increased vessel permeability) and airways (bronchoconstriction).

Reactions that are similar but caused by an antibody-independent mechanism are variably termed anaphylactoid, pseudo-allergic and idiosyncratic reactions. Current terminology, provided by the European Academy of Allergy and Clinical Immunology, differentiates these reactions by using the phrases allergic and non-allergic anaphylaxis. Non-allergic reactions were thought to have relatively mild clinical severity (Mertes et al. 2003) but it is now recognised that these are clinically indistinguishable from those that are IgE mediated. Classically, a non-allergic reaction was presumed if it occurred at first exposure, whereas allergic anaphylaxis was thought only to occur in patients previously exposed to the causative drug. However, because of cross-reactivity of IgE receptors between drugs and similar chemicals encountered elsewhere, this differentiation is also incorrect. Fulminant allergic anaphylaxis can occur at first exposure to neuromuscular blocking agents if the patient is already sensitised to similar chemicals in toothpaste, detergent and cough medications. Similarly, lack of prior exposure to latex does not preclude allergic anaphylaxis, due to links to certain fruit allergies.

The mechanisms behind non-allergic anaphylactic reactions are less well understood and more variable than IgE-mediated anaphylaxis, and are reviewed more fully in Descotes et al. (2007). Direct histamine release is frequently thought to be the most important mechanism, however there are likely many others, including complement-mediated processes. Direct drug-induced histamine release may be via interaction with mast cell membrane receptors, or be mediated by receptor-independent mechanisms. The clinical observation that most of these reactions only occur following intravenous

drug administration (and are more severe the more rapidly the drug is administered) led to suggestions of osmotic or ionic gradient effects. Histamine release induced by hyperosmolar stress has been presented as an explanation for reactions to hyperosmolar radiocontrast media. Opioids (and other basic compounds) cause histamine release by binding non-opioid-specific mast cell G-protein receptors, activation of which leads to an increase in intracellular calcium concentration and mast cell degranulation (Barke & Hough 1993). Acute changes in transmembrane gradients of sodium and chloride ions induced by other agents may have similar histamine-releasing effects.

Activation of the complement cascade has an important role in anaphylaxis. The complement system is comprised of a number of proteins that are sequentially activated during immune system activation, resulting in mast cell degranulation, inflammatory cell chemotaxis, increased vascular permeability and smooth muscle contraction. The classical pathway, activated by antigen-antibody complexes, is generally activated by IgG and IgM and therefore is probably not of major importance in drug reactions. In contrast, the alternate pathway is likely of major significance to non-immune anaphylaxis, as it can be triggered directly by a number of drugs. Cremophor and certain radiocontrast media are examples of exogenous agents able to directly activate the complement cascade; these agents cause spontaneous hydrolysis and activation of complement protein C3, leading to production of anaphylotoxins C3a, C4a and C5a, potent stimulators of histamine release and vascular leakage.

The pathogenesis of non immune anaphylaxis is further complicated by the observation that different mechanisms can be involved in reactions to an individual drug. This is of particular relevance because of the varied explanations for reactions to Althesin (alphaxolone-alphadolone in Cremophor) in people (Radford et al. 1982). In some patients, the observed reaction was consistent with Cremophor-induced complement activation. However other reactions differed in their immunology, prompting fears by some that a direct drug effect may be involved (Glen et al. 1979).

A further degree of complication is added to our understanding of anaphylaxis by the variability that occurs between species. When known histamine-liberators are added to mast cells of different species, variability in the magnitude of histamine release is

seen (Pearce 1982). The response to Cremophor differs greatly in mast cells from pigs, dogs, cats and humans, probably explaining the differences observed clinically when dogs and cats are administered Cremophor-based alphaxolone-alphadolone (Saffan).

Whether mediated by IgE or non-IgE mechanisms, clinical manifestation and emergency management of anaphylactic responses are the same. The Ring and Messmer clinical severity scale is useful for describing the clinical response, and for guiding patient management (Ring & Messmer 1977). Grade 1 and 2 responses (cutaneous signs, and non life-threatening tachycardia, hypotension, dyspnoea or gastrointestinal disturbance respectively) usually occur first, and are followed by life-threatening cardiovascular or respiratory changes (grade 3) and cardiac arrest (grade 4). However, deviations from this model are common, and variations do not preclude an allergic-type drug reaction – in rapid and severe cases (generally the more rapid a response the higher the clinical severity) grades 1 and 2 are usually absent or missed. This is particularly the case in anaesthetised veterinary patients, where hair, drapes and anaesthetic agents mask some of the initial changes. In a small percentage of cases, sudden bradycardia may be the first sign of a problem – this is a result of the Bezold-Jarisch cardiac reflex and is a response to sudden, dramatic hypovolaemia caused by fluid extravasation. The slowing of the heart is likely a protective response to allow the ventricles to fill during severe volume deficit, and rapid volume expansion rather than anticholinergic administration is therefore the most appropriate management. In severe (grades 3 and 4) cases management consists of administration of titrated doses of epinephrine, rapid volume expansion and airway management, with provision of 100% oxygen. Less aggressive fluid management, oxygen supplementation and symptomatic management of gastrointestinal disturbance is usually sufficient for grade 2 reactions, and grade 1 responses frequently do not require therapy. The presumed causative agent should be withdrawn; in the anaesthetised patient, where multiple drugs are frequently being given simultaneously, this may involve stopping the administration of all anaesthetic and other agents (where practical), since it may not be apparent which is the problem drug. Bronchoconstriction can be managed using inhaled or parenteral beta agonists, however this is usually unnecessary if adrenaline has been administered. Corticosteroids

and histamine blockers are often considered at this stage, however there is little evidence to support their efficacy in severe reactions (Dewachter et al. 2009).

Which agents are likely to cause a life-threatening response? The reality is that almost any agent can cause a reaction, however some are implicated more than others. Published reports of anaphylactic reactions in veterinary patients are surprisingly rare – a Pubmed search performed for the purpose of this editorial yielded less than 25 clinical reports published since 1950, most of which described reactions to antibiotics and vaccines, with isolated reports of reactions to thiopental, acepromazine, meperidine, xylazine-ketamine and iodinated contrast agents (Baer et al. 1962, Mason 1976, Waechter 1982, Davis 1984, Clutton 1987, Raptopoulos et al. 1993, Kushner & Trim 1994, Meyer 1997, Pollard & Pascoe 2008). This makes determining the risks of anaphylaxis difficult to assess, as the likelihood is that many more reactions have been observed, but go unreported for a variety of reasons. Particularly during anaesthesia, when several drugs are administered concurrently, it is difficult to identify which agent the patient reacted to. Even if a reaction to a particular drug is strongly suspected, this is unlikely to be published given the inability to specifically document the reaction, the limited number of journals that publish case reports, and the frequent requirement for the reaction to be a 'first reported case'. Because of the rarity of reactions, retrospective studies would need to involve vast numbers of patients for incidences and risk to be accurately calculated. As shown by the study in this issue (Mair et al., 2010), it is extremely difficult to document anaphylactic reactions in a prospective fashion.

So what of preventative measures? Much literature in people discusses whether there is an increase in risk of IgE-mediated reactions in patients with other allergic diseases. Airway signs will be more severe in patients with pre-existing airway diseases, including those with an allergic component such as asthma. However, there is no evidence that such patients are more likely to suffer an anaphylactic reaction. Dogs frequently present with a history of food allergies, including evidence of hypersensitivity to soy proteins (Jackson et al. 2003). However, whether hypersensitivity to dietary soy increases the risk of a reaction to soy lecithin found in propofol formulations is unknown. In people, documented

egg allergy is not thought to increase the risk of a reaction to propofol, despite soy-lecithin formulations containing purified egg protein (Hepner & Castells 2003). Various companies offer allergy testing, either by serological or via intradermal skin injections. However the association between the results of such tests and the risk of a drug reaction is poor, and various tests have either a low specificity or low sensitivity for the diagnosis or prediction of drug reactions (Hepner & Castells 2003). Such testing is most accurate when performed after an anaphylactic event; it must be carried out within 4–6 weeks, due to possible depletion of IgE, mast cell or basophil levels, and may be of some use in documenting hypersensitivity to a particular agent following a reaction during the anaesthetic period. However, even a positive result may not necessarily predict a future adverse reaction, since such results may be indicative merely of previous exposure and not necessarily hypersensitivity.

Preventative measures rather than predictive testing are therefore most likely to be useful in a patient with a history of a previous reaction (for example a patient referred because it had a previous, unexplained reaction to an anaesthetic). In this situation, exclusion of the causative agent is preferable, but the identity of the agent may not be certain. Recommendations from the human literature suggest using local or regional anaesthesia instead of general anaesthesia if possible (and if local anaesthetics are not suspected in the aetiology of the prior response), and suggest that volatile agents are preferred to injectable anaesthetics, because anaphylactic reactions to volatile anaesthetics have not been reported. If such information is available, it is advisable to avoid all agents administered during the previous anaesthetic period, not just the agent suspected of causing the reaction. Pretreatment with antihistamines and corticosteroids is widely practised, but there is little evidence that these are helpful and they definitely do not prevent a severe anaphylactic response (Kroigaard et al. 2007, Liccardi et al. 2008). The most important management consideration for such patients is therefore to be alert to the signs of anaphylaxis, and to have immediately available the fluids, epinephrine, airway kit and oxygen required to treat such a reaction. Given the reports of systemic responses to gadolinium-based contrast agent in this issue, it would seem pertinent to employ such considerations to patients undergoing contrast CT scans.

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