



Hypersensitivity reactions in the anesthesia setting/allergic reactions to anesthetics

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Purpose of review

Immediate hypersensitivity reactions are an important cause for mortality and morbidity in anesthesia. The present review considers reports covering epidemiology, diagnosis, and treatment of these reactions.

Recent findings

Immediate hypersensitivity reactions are largely under-reported, adult women being at significantly higher risk than men. The role of sex hormones associated with increased risk in adult women has been demonstrated. Neuromuscular blocking agents (NMBAs) remain the most frequently incriminated drugs. Reactions involving antibiotics, dyes, or nonsteroidal anti-inflammatory agents are reported with increasing frequency, in parallel with changing trends in clinical practice. A recent hypothesis concerning a link between pholcodine exposure and allergic reactions to NMBAs is under investigation. Detailed guidelines concerning skin testing have been provided. The use of several inotropes or vasopressor such as vasopressin is proposed in case of reactions refractory to epinephrine and volume expansion. The use of cyclodextrin to mitigate severe allergic reactions to rocuronium, by specific drug encapsulation, has been proposed.

Summary

Hypersensitivity reactions remain a major cause of concern in the perioperative setting. Although largely under-reported, their incidence is higher than previously reported. NMBAs remain the most frequently incriminated drug, followed by latex and antibiotics. The number of reactions involving new allergens like vital dyes or nonsteroidal anti-inflammatory drugs is rapidly increasing. The mechanism of sensitization to NMBAs could be influenced by as yet unidentified environmental factors. The possible role of pholcodine is under investigation. Several guidelines concerning the diagnosis and management of immediate hypersensitivity reactions in anesthesia are now available.

Keywords

anaphylaxis, anesthesia, epinephrine, neuromuscular blocking agent, skin test, tryptase

INTRODUCTION

Anesthesia is the medical specialty which ensures optimum operative conditions for both the patient and for the surgeon. Although its practice has grown increasingly safe, the perioperative setting represents a pharmacologically unique situation, during which patients are exposed to multiple foreign substances including anesthetics, analgesics, antibiotics, antiseptics, blood products, heparin, polypeptides, and intravascular volume expanders, which have the potential to produce a variety of predictable and unpredictable adverse reactions. As a consequence, anesthetists are more likely than most other physicians to witness and manage immediate hypersensitivity reactions or anaphylaxis, which sometimes occur during anesthesia. The effective anticipation, prevention, and treatment of these reactions are critical to reduce overall

mortality and morbidity related to anesthesia. It is largely dependent on the knowledge and vigilance of the attending clinicians and on subsequent allergological investigations to identify the offending agent and prevent recurrences, since no preemptive therapeutic strategies exist. This review covers

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KEY POINTS

- The incidence of IgE-mediated hypersensitivity reactions during anesthesia has been estimated at 100.6 (76.2–125.3) per million procedures.
- The increased risk of allergic reactions to anesthetics in women appears to be influenced by sex hormones.
- The hypothesis of a role of a prior exposure to pholcodine in sensitization to neuromuscular blocking agents is under investigation.
- Vasopressin has been proposed as a rescue treatment in anaphylaxis resistant to epinephrine and volume expansion.
- The potential interest of rocuronium encapsulation by the cyclodextrin sugammadex to mitigate immediate allergic reaction is under investigation.

recent data on the epidemiology, pathophysiology, clinical features, diagnosis, and management of anaphylaxis associated with anesthesia.

A Medline search was performed for articles using the key words (anesthesia) AND (allergy) published in the period 2009 to 2012. We made a critical selection relevant to the topic, and added important references from this time period that were identified using related articles or additional specific key words such as antibiotics, vasopressin, cyclodextrins, pholcodine, tryptase, nonsteroidal anti-inflammatory drug and contrast media.

EPIDEMIOLOGY

Adverse drug reactions have been recognized as one of the most common causes of morbidity and death in anesthesiology practice. Therefore, increasing attention has been paid over these past decades to immediate hypersensitivity reactions or anaphylaxis that may occur during the very vulnerable perioperative period. One of the obvious weaknesses of any review of epidemiologic studies of such reactions is the lack of consensus definition, the heterogeneous use of terms in the literature, and the absence of clear insight into underlying pathophysiologic mechanisms. Although often clinically indistinguishable, immediate hypersensitivity reactions can be either immune-mediated (allergic) or nonimmune-mediated (pseudoallergic or anaphylactoid reactions) [1].

IgE-mediated and non-IgE-mediated reactions

The true incidence of immediate hypersensitivity reactions is usually regarded as poorly defined as a

result of uncertainties about reporting accuracy and exhaustiveness. Nevertheless, over the past decades, a long-term policy of systematic clinical and/or biological investigation of immediate hypersensitivity reactions carried out in France, the UK, New Zealand and Australia, and Denmark and Norway has produced a relatively coherent picture of the problem. This information has been summarized in several good-quality reviews [2[•],3[•]].

Despite reported variations, probably reflecting differences in clinical practice and reporting systems, the overall incidence of immediate hypersensitivity reactions from all mechanisms seems to be similar between countries, ranging from 1 in every 1250 to 10 000 anesthetics [2[•]].

Significant progress has been made in the characterization of IgE-mediated hypersensitivity reactions. In most series, allergic reactions represent at least 60% of all hypersensitivity reactions observed within the perioperative period. Recently, a combined analysis of three different French databases, using a capture-recapture method, has allowed a nationally based estimate of the incidence of immediate IgE-mediated allergic reactions occurring during anesthesia, stratified according to sex, age, and causal substance. The capture-recapture method represents a helpful tool for incidence estimation when several independent sources of information are available. Cases identified by each source should be real cases, identified in the same population, within the same geographic area, and during the same period. The intersection of the different data sources identifies the number of common cases which can be used to estimate the number of unreported cases. This study has confirmed the general view that immediate-type hypersensitivity reactions are largely under-reported, with the incidence of allergic reactions being estimated at 100.6 (76.2–125.3) per million procedures (Table 1) [4[•]].

Almost all the drugs and substances to which patients are exposed perioperatively have been known to cause allergic reactions. In all series, neuromuscular blocking agents (NMBAs) represent the most frequently incriminated substance ranging from 50 to 70% (Table 1) [2[•]–4[•],5]. The frequency of allergic reactions to latex largely depends on the local prevention policy applied in each institution [2[•]–4[•],6,7]. Reactions involving antibiotics are mainly due to penicillins and cephalosporins. These reactions have rapidly increased in the past decade, reflecting the increasing prevalence of allergy to these drugs in the general population as well as their increased use in perioperative antibiotic prophylaxis [2[•],4[•],5,8]. Hypnotic agents, opioids, colloids, aprotinin, and protamine are less frequently attributed, whereas cases involving dyes, chlorhexidine,

Table 1. Estimated annual incidence of IgE-mediated allergic reactions during anesthesia

Causal agent	Estimated annual number of case	Estimated annual incidence (per million) median (5th–95th percentile)		
		Male	Overall	Female
Overall	780 (555–1005)	55.4 (42.0–69.0)	100.6 (76.2–125.3)	154.9 (117.2–193.1)
Neuromuscular blocking agents	458 (326–590)	105.5 (79.7–132.0)	184.0 (139.3–229.7)	250.9 (189.8–312.9)
Latex	155 (110–200)	32.6 (24.7–40.5)	59.1 (44.8–73.6)	91.0 (68.9–113.4)
Antibiotics	101 (72–131)		–	
Other agents	80 (57–103)		–	

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or nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported with increasing frequency [2^{***}–4^{***},5,9,10]. Allergy to local anesthetics appears truly uncommon [2^{***}–4^{***},11,12,13^{*}].

Epidemiology in children, sex ratio

In children, the various incriminated substances differ significantly from those for adult patients. The largest published study [4^{***}] of allergic reactions in the perioperative period originates from France. In this series comprising 266 cases, allergic reactions were diagnosed in 45% of cases. Latex was the most frequently incriminated substance (51 cases; 41.8%), followed by NMBA (39 cases; 32%) and antibiotics (11 cases; 9%).

Interestingly, this study also provides a very attractive hypothesis to explain the female predominance reported in all series [2^{***},3^{***}]. Indeed, in contrast with the results observed in adults, no significant differences were observed in regard to the sex distribution in children for both IgE-mediated or non-IgE-mediated reactions. This similar incidence of allergic and nonallergic reactions according to sex before adolescence strongly suggests a role for sex hormones in the increase of immediate hypersensitivity reactions to low-molecular-weight compounds observed in women after puberty.

ORIGIN OF IGE ANTIBODIES TO NEUROMUSCULAR BLOCKING AGENTS: THE PHOLCODINE HYPOTHESIS

Allergic reactions to NMBA are almost exclusively IgE-mediated. Therefore if an individual develops anaphylaxis to an NMBA, this implies the presence of specific IgE antibodies on his mast cells and basophils at the time of exposure and reaction. However, up to 75% of reactions have been reported upon first known contact with an NMBA [2^{***},3^{***}].

This suggests a possible cross-reaction with IgE antibodies generated by previous contact with apparently unrelated chemicals. Structure-activity studies have established that the substituted ammonium groups present on each NMBA are part of the allergenic determinant structure [14]. Since compounds containing tertiary and/or quaternary ammonium groups occur widely in the human environment in drugs, cosmetics, disinfectants, industrial materials, or foods, it has been suggested that sensitization to NMBA may occur via these sources. However, the hypothesis of the theory of environmental sensitization remains as yet unproven [14].

Recently, Florvaag and Johansson [15] pointed out that anaphylaxis to NMBA was 10 times more common in Norway than in Sweden. They suggested that this difference could be due to differences in preoperative sensitization in relation to pholcodine consumption [15]. They reported that during the 1970s and 1980s cough syrup containing this drug was available in Sweden, whereas IgE antibodies to pholcodine were present in 5–6% of sera collected during the same time period. No positive sera were found since 2005 following its withdrawal from the market. They also reported that the number of cases of anaphylaxis to NMBA was high in the 1970s in Sweden, whereas no case was reported after 1990. They later demonstrated that pholcodine exposure in patients having experienced an allergic reaction to an NMBA was responsible for a significant increase in specific IgEs to NMBA in patients having experienced an allergic reaction to one of these drugs. This led to the hypothesis that pholcodine exposure could either lead to IgE-sensitization to this drug and other quaternary ammonium ions or increase the titer of specific IgEs to quaternary ammonium ions and thereby increase the risk of allergic reaction to NMBA. This hypothesis was further supported by the results of an international prevalence study, showing a statistically significant association between pholcodine consumption and

prevalence of IgE-sensitization to this drug and to succinylcholine. However, the results also indicate that other, yet unknown, substances may be involved in IgE-sensitization towards NMBAs. Withdrawal of pholcodine from the Norwegian market resulted in the decrease of IgEs to quaternary ammonium ions in the population and in the number of reports of allergic reactions to NMBA [16²²]. These results strongly support the need for further epidemiological studies designed to investigate the possible link between pholcodine exposure and hypersensitivity reactions to NMBAs.

EMERGING ALLERGENS

Although NMBAs, latex, and antibiotics remain the most frequently incriminated substances, reactions involving new allergens are reported with an increasing frequency.

NSAIDs

Within the past decade, an increasing use of non-steroidal anti-inflammatory agents as part of post-operative multimodal analgesia has been observed. This has led to an increased number of immediate hypersensitivity reactions, although mostly non-IgE-mediated, in the perioperative setting [4²³]. A recent update from the European Academy of Allergy and Clinical Immunology/European Network for Drug Allergy [17²⁴] proposed a step-wise approach to the diagnosis of hypersensitivity to NSAIDs, including clinical history, and drug provocation test (DPT) with the culprit or alternative NSAID depending on the type of the reaction. Skin tests to NSAIDs are rarely indicated in the perioperative setting, and cases of IgE-mediated reactions are amongst the exceptions. Urticaria, angioedema, and/or anaphylaxis can indeed be induced by a single NSAID or a group of closely chemically related compounds. With the exception of hypersensitivity to pyrazolones and paracetamol, most studies reporting single drug reactions are case reports [18]. Given the variety of clinical presentations of NSAID hypersensitivity (respiratory, cutaneous, or anaphylaxis; and single or multiple reactors), reliability of clinical history at the preoperative consultation may be difficult to assess, and some patients may require DPTs to confirm or refute the diagnosis [19²⁵]. However, for those with typical presentations (such as asthmatic reaction, multiple reactions to multiple NSAIDs, or anaphylaxis to a single NSAID), DPT is mostly needed to confirm tolerability of alternative compounds, particularly to potent or cyclooxygenase inhibitors in single responders [20²⁶].

Iodinated contrast media

Immediate hypersensitivity reactions to iodinated contrast media (ICM) are relatively rare in the perioperative period. They are mainly observed prior to surgery during radiologic investigations in emergency situations or during anesthesia outside the operating room. Skin tests are a useful tool in the allergy work-up of hypersensitivity to ICM, but data concerning their negative predictive value are scarce. In a retrospective study [21] involving 120 patients tested for a compatible clinical history of ICM-induced hypersensitivity, 29 patients with initial negative skin tests needing a new ICM injection were re-challenged without premedication. One patient out of 24 with a history of immediate, and 1 out of 4 with a history of nonimmediate reaction, presented with mild reactions upon re-challenge. Two patients with positive ICM skin tests tolerated an alternative ICM without any adverse reaction. Overall, the negative predictive value of skin testing for ICM was 96% and none of the reactions was severe. However, further studies involving a larger number of participants are required.

Dyes

The extensive use of the triarylmethan dyes patent blue V and isosulfan blue in lymphatic mapping for sentinel node biopsy has been incriminated in a significant number of cases of hypersensitivity reactions [22–25]. Sensitization may originate from the widespread use of these dyes in cosmetics and other everyday life objects. Since anaphylactic reactions involving methylene blue seem less common, it has been proposed as a possible alternative [25,26]. However, immediate hypersensitivity reactions to viro-inactivated fresh frozen plasma inactivated with methylene blue has recently been reported [27].

The clinical diagnosis of reactions elicited by dyes is difficult. Reactions are usually delayed (i.e. 30 min following injection), long-lasting, and justify prolonged monitoring in intensive care if prolonged epinephrine administration is necessary [10,23].

The mechanism underlying hypersensitivity reactions to blue dyes remains unclear. Direct mast cell and/or basophil activation and cross-linking of specific IgE antibodies are possible causative factors. Reactions can be investigated by skin and basophil activation tests [28,29], strongly suggesting an IgE-mediated mechanism. The use of intradermal tests in cases of negative prick test is recommended [23]. Although methylene blue differs structurally from isosulfan blue and patent blue V, several cases of

sensitization to patent blue and methylene blue have been reported. Intradermal and basophil activation tests may also facilitate identification of potentially cross-reactive and better tolerated alternative dyes.

Chlorhexidine

This antiseptic and disinfectant is widely used in mouthwashes or for disinfection of minor scratches. Cases of allergic reactions are regularly reported [5,9]. Clinical diagnosis may be difficult in cases related to the use of chlorhexidine-bound central venous catheters or as lubricants for urinary catheterization, and should be confirmed by skin tests and/or commercially available specific IgE assay.

Ethylene oxide

This reactive gas is widely used to sterilize heat-sensitive medical devices. Ethylene oxide has long been recognized as a possible sensitizing agent, particularly in spina bifida patients, frequently in association with sensitization to latex [5]. The clinical significance of IgEs recognizing ethylene oxide has sometimes been questioned. A renewed interest in this possible sensitizing compound has emerged in the recent literature [30,31].

Blood products

Although rare, anaphylactic reactions can occur after the transfusion of any blood product. They are likely to be observed in the perioperative setting since half of the blood products transfused are administered in surgical patients. Mild reactions such as urticarial reactions and generalized pruritus are common, occurring during approximately 1–3% of all transfusions, whereas severe allergic reactions occur in 1 in 50 000 transfusions [32]. The pathophysiology of these reactions remains poorly understood, insufficiently investigated, and complicated by its multifaceted nature. Three mechanisms have been described: recipient-related, donor-related, and blood-related [33]. In recipient-related reactions, antibodies of the recipient may react with an allergen contained in the blood product [34]. This is typically the case with anti-IgA in a patient with IgA deficiency, or with free or plasma protein-bound molecules such as food or drug allergens transfused in a previously sensitized patient. In donor-related reactions, the transfused blood product may contain the antibodies or the lymphocytes of a sensitized donor and will trigger a reaction in the recipient if he/she is then exposed to the allergen [35]. In blood-related reactions, the blood

product transfused may contain mediators accumulated during storage that may trigger a reaction mimicking allergy.

Evaluation of severe anaphylactic reaction classically includes recipient testing for IgA and anti-IgA antibodies in cases of IgA deficiency. The interest in histamine and tryptase measurements at the time of the reaction and of basophil activation tests to further investigate the mechanism of the reaction has recently been advocated [33,36]. Delayed investigations consisting of skin tests to methylene blue (prick and intradermal) and of basophil activation test has been found useful for the diagnosis of allergic reaction to methylene blue viro-attenuated fresh frozen plasma [27].

Plasma removal from platelet concentrates and red blood cells through concentration or washing has been proposed to decrease the incidence of anaphylactic reactions [37,38], whereas premedication has been found to be ineffective [39].

DIAGNOSIS

Several excellent guidelines for the investigation of suspected anaphylaxis have been recently published by anesthesiology and/or allergy societies [7,40,41[■]].

Serum tryptase

Serum tryptase measurements are recommended in every guideline. Serum tryptase levels show only small intraindividual variation in the absence of anaphylaxis [42]. Although a rise in serum tryptase simply indicates mast cell degranulation and does not discriminate between allergic and nonallergic anaphylaxis, it has been proposed that increased tryptase concentrations exceeding 25 mcg/l suggests an IgE-mediated mechanism. However, in mild reactions limited to mucocutaneous symptoms, the concentrations are often normal and tend to be only slightly elevated if the systemic reaction is moderate. The recommended time points to measure tryptase are: a first sample taken immediately after resuscitation, a second sample at 1–2 h, and a baseline sample at 24 h or any time after this. In the case of fatal reactions, the sample should preferably be taken before abandoning resuscitation rather than after death [41[■],43]. Increased concentrations in basal tryptase unrelated to the allergic incident may be observed in patients with systemic mastocytosis, mast cell activation syndrome, or hematologic diseases. A possible heterophilic antibody interference caused by rheumatoid factor interfering with tryptase measurement has recently been reported [44].

Tests to identify the causative agent

The purpose of allergy investigations is to identify the drug or substance responsible and the mechanism behind the reaction, to make subsequent anesthesia or further drugs intake as well tolerated as possible.

In-vitro tests

Significant progress has been made with in-vitro testing. These mainly concern specific IgE measurements and basophil activation tests (BATs).

Radioimmunoassays [Radio Allergo Sorbent Test (RAST)] are progressively being replaced by non-radioactive and more automated methods [45,46]. However, the availability of these tests for the range of drugs and agents involved in perioperative anaphylaxis remains limited. NMBA, latex, thiopental, chlorhexidine, and some antibiotics are the few classes of drugs for which these tests are available [41¹¹]. These tests can be performed at the time of the reaction or can be delayed.

Basophil activation assays (histamine release assay, basophil activation test: BAT, and leukotriene release test) have been proposed as possible assays to use to investigate hypersensitivity reactions. These tests may be used when skin test results are difficult to interpret or when skin testing is not possible. Although not currently widely used, these tests seem to have a good specificity and have been successfully used in several situations [27,47].

Skin tests

Skin tests coupled with history remain the mainstay of diagnosis of IgE-mediated reactions. Detailed recommendations on the maximum concentration to be used for most of the drugs and substances used in the perioperative period have been published [41¹¹]. Skin prick and/or intradermal tests are usually performed 4–6 weeks after the acute reaction [41¹¹]. Recent recommendations suggest that skin testing can be performed immediately after a reaction. However, there is a small amount of safety data to provide confidence in early skin testing, and in such cases, only positive skin tests are useful as false-negative tests cannot be excluded [48].

In view of frequent but not systematic cross-reactivity observed among muscle relaxants, all available NMBA should be tested in the evaluation of allergy to one of these drugs in an attempt to identify nonreactive compounds which the patient could use as alternatives. Although no diagnostic procedure is devoid of false-positive or false-negative results, this practice may help to provide

documented advice for the future choice and administration of anesthetic agents [49,50].

TREATMENT

The cornerstones of treatment for hypersensitivity reactions during anesthesia are epinephrine and fluid therapy, as recommended in all published guidelines [7,41¹¹,51]. During anesthesia, the patient is usually monitored and has intravenous access, which provides the optimum conditions for prompt intravenous epinephrine administration, provided that the diagnosis is made early by the attending anesthetist [52¹²]. However, there is a wide array of reaction severity and response to treatment. Therefore, epinephrine administration should be tailored to the severity of symptoms.

In addition, no controlled trials of treatment of hypersensitivity reactions during anesthesia in human beings are available. Thus, the use of a large diversity of vasopressors and inotropes such as nor-adrenaline, vasopressin, methylene blue, or glucagon has been proposed when initial resuscitation with epinephrine and fluids is not successful [53].

Several recent case reports suggest that administration of sugammadex, a chemically modified gamma-cyclodextrin used for rapid reversal of rocuronium-induced neuromuscular blockade, might be useful in mitigating rocuronium-induced anaphylaxis [54¹³,55]. However, several theoretical and experimental objections to the likelihood of an allergen-binding agent being able to attenuate the immunological cascade of anaphylaxis have been raised [56¹⁴,57¹⁵,58¹⁶]. On the contrary, allergic reactions to sugammadex have also been reported [59].

If the efficacy of sugammadex is further confirmed, the possibility of encapsulating and removing other allergenic drugs should be considered as a new therapeutic approach in cases of intractable anaphylaxis.

CONCLUSION

Perioperative anaphylaxis remains an important cause of morbidity and mortality during anaesthesia. NMBA, latex, and antibiotics are the most frequently incriminated drugs, although other drugs used during the perioperative period might be involved. Any suspected hypersensitivity reaction must be extensively investigated using combined perioperative and postoperative testing, according to well established guidelines.

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None.

Conflicts of interest

The authors have no conflict of interest to declare.

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 441).

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