Anesthesia in the patient with multiple drug allergies: are all allergies the same?

Pascale Dewachter[a], Claudie Mouton-Faivre[b], Mariana C. Castells[c] and David L. Hepner[d]

[a]Pôle d'Anesthésie-Réanimation, Hôpital Gabriel Montpied, Clermont-Ferrand, [b]Pôle d'Anesthésie-Réanimation Chirurgicale, CHU Hôpital Central, Nancy, France, [c]Division of Rheumatology, Immunology and Allergy, Department of Medicine and [d]Department of Anesthesia, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Correspondence to Pascale Dewachter, MD, Centre Hospitalier Universitaire, Pôle d'Anesthésie-Réanimation Chirurgicale BP 69, 63003 Clermont-Ferrand Cedex 1, France
Tel: +33 4 73 75 15 90;
e-mail: pascale.dewachter@yahoo.fr

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Purpose of review

During the preoperative evaluation, patients frequently indicate 'multiple drug allergies', most of which have not been validated. Potential allergic cross-reactivity between drugs and foods is frequently considered as a risk factor for perioperative hypersensitivity. The aim of this review is to facilitate the recognition of risk factors for perioperative anaphylaxis and help the management of patients with 'multiple drug allergies' during the perioperative period.

Recent findings

Neuromuscular blocking agents (NMBAs) and antibiotics are the most common drugs triggering perioperative anaphylaxis. Quaternary ammonium ions have been suggested to be the allergenic determinant of NMBAs. Even though the 'pholcodine hypothesis' has been suggested to explain the occurrence of NMBA-induced allergy, this concept remains unclear. Although many practitioners believe that certain food allergies present an issue with the use of propofol, there is no role to contraindicate propofol in egg-allergic, soy-allergic or peanut-allergic patients. IgE-mediated hypersensitivity has been reported with seafood and iodinated drugs, IgE-mediated hypersensitivity has been reported with seafood and iodinated drugs, but there is no cross-reactivity between them. The allergenic determinants have been characterized for fish, shellfish and povidone iodine and remain unknown for contrast agents.

Summary

There are many false assumptions regarding drug allergies. The main goal of this article is to review the potential cross-reactivity among specific families of drugs and foods in order to facilitate the anesthetic management of patients with 'multiple drug allergies'.

Keywords

anesthesia, drug hypersensitivity, food hypersensitivity

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Introduction

During the preoperative evaluation, patients frequently indicate 'multiple drug allergies'. Such statement may lead to a difficult perioperative management by the anesthesiologist in charge. The concept of 'multiple drug allergy syndrome' is defined by a propensity to react against different chemically unrelated antibiotic or non-antibiotic drugs [1]. However, there is disagreement about what constitutes a true allergic reaction. Immediate hypersensitivity reactions now encompass IgE-mediated and non-IgE-mediated reactions. Allergenic cross-reactivity is a property defined by individual antibodies to other allergens with structural similarity and can be seen in families of drugs or agents used during the perioperative period. The aim of this review is to provide guidance for practitioners by reviewing the clinical presentation pattern of patients with 'multiple drug allergies' and help establish evidence, or refute false beliefs, of cross-reactivity for drugs used during anesthesia to facilitate the perioperative management of these patients.

Immediate allergic hypersensitivity to anesthetic drugs

Immediate hypersensitivity is a syndrome that varies in severity and is associated with clinical features which include cardiovascular, respiratory and mucocutaneous signs, as described according to the Ring and Messmer four-step grading scale. By definition, an immediate hypersensitivity reaction occurs within a few minutes to 60 min following the injection or introduction of the culprit agent [2•]. Immediate hypersensitivity reactions are subdivided into allergic and nonallergic hypersensitivity (in which an IgE-mechanism is excluded) [3]. Immediate allergic hypersensitivity is a reaction triggered

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by specific immunological mechanisms mediated by antibodies (usually IgE isotype antibodies) and can lead to life-threatening symptoms [3]. If possible, the diagnosis of perioperative drug-induced anaphylaxis should be confirmed by an appropriate allergological assessment [2•,4,5,6••]. The initial diagnosis is clinical and remains presumptive but tryptase levels can confirm mast cell activation at the time of the reaction and skin testing can identify the allergen. During the perioperative period, the most common drugs triggering IgE-mediated anaphylaxis are neuromuscular blocking agents (NMBAs) and antibiotics [2•].

'Multiple drug allergy syndrome' or cross-reactivity?

'Multiple drug allergy syndrome' or 'multiple drug hypersensitivity' is a clinical condition characterized by a propensity to react against different chemically unrelated drugs, mainly antibiotics [1]. In most cases, the syndrome presents as acute urticaria, angioedema or both upon administration of offending compounds [1]. Nevertheless, the existence of the 'multiple drug allergy syndrome' remains highly debated. To some, this rare entity does not constitute a syndrome but applies to particular individuals [7,8]. False assumptions regarding allergic cross-reactivity between different drugs and/or food (e.g., seafood) is frequently evoked in clinical practice and improperly considered as a risk factor for perioperative allergic reactions. Allergenic cross-reactivity is a prominent feature of the IgE response and reflects the phylogenetic relations between organisms [9]. Two allergens with common or similar epitopes can be recognized by a single antibody and sensitization to one allergen can cross-sensitize a patient to the other without direct exposure. Cross-reactivity has been described with NMBAs, antibiotics, iodinated contrast agents and certain foods, and refers to allergens with structural similarities (i.e., a high degree of homology) in the primary structure of the amino acid sequence in some cases. Protein glycosylation patterns have also been seen as inducing cross-reactivity [10]. Galactose alpha 1,3 galactose antibodies have been found in patients with reactions to cetuximab, a monoclonal antibody approved for use in colorectal and head and neck squamous-cell cancer, and beef in the southern USA states indicating cross-reactivity between cetuximab and beef allergens [10].

Risk factors for immediate allergic hypersensitivity to anesthetic drugs

The main risk factor for perioperative anaphylaxis to anesthetic drugs is a previous uninvestigated severe immediate hypersensitivity during the perioperative period. An allergological assessment should be performed prior to the surgical procedure, if possible [2•,5,6••].

Key points

- Clinical symptoms are the most important piece for the evaluation of adverse drug reactions and an allergic evaluation is mandatory for all immediate hypersensitivity reactions.
- Tryptase levels should be investigated whenever possible during immediate hypersensitivity, because it documents mast cell activation.
- There are no data to support the avoidance of propofol in patients with egg allergy, soy allergy or peanut allergy.
- There is no cross-reactivity between povidone iodine, iodinated contrast media and shellfish.
- The main risk factor for perioperative anaphylaxis is a previous immediate perioperative reaction.

Cross-reactivity and drugs used during the perioperative period

It is important for the anesthesiologist to understand whether cross-reactivity within the same or a similar group of medications does really exist, as a potential hypersensitivity reaction may be life threatening. In addition, many food allergies are often mistakenly considered a contraindication to some medications, making the anesthetic plan more challenging. Therefore, an understanding of the cross-reactivity of drugs utilized during the perioperative period is quite important.

Neuromuscular blocking agents

NMBAs are involved with perioperative IgE-mediated anaphylaxis in 50–70% of cases according to epidemiological studies conducted in Australia and Europe [2•,4,6••]. All NMBAs may elicit anaphylaxis, and cross-reactivity between NMBAs is common in approximately 60–70% of cases [2•,4,5,6••]. For more than 20 years, the quaternary ammonium ions have been suggested to be the allergenic determinants by binding to the ammonium groups in-vitro immunoassay studies performed with sera from patients having experienced NMBA-induced anaphylaxis [11]. From a clinical point of view, cross-reactivity among all NMBAs would be the rule, as all NMBAs share the quaternary ammonium ions. However, despite a previous documented NMBA-induced anaphylaxis, negative skin-tested NMBAs may be safely utilized [12,13•], as supported by various guidelines on perioperative anaphylaxis [6••,14]. Currently, the only known risk factor for NMBA-induced anaphylaxis is a previous undocumented immediate hypersensitivity reaction that occurred during a prior anesthetic conducted with a NMBA. Nevertheless, uneventful previous exposure to a NMBA does not exclude the risk for IgE-mediated anaphylaxis during a subsequent anesthetic [2•,6••]. In addition, anaphylaxis to NMBAs may occur in patients without a prior

NMBA exposure [2•,6••,11], the mechanism for this sensitization remains unknown.

The pholcodine hypothesis

A few years ago, a higher prevalence of IgE antibodies to tertiary and/or quaternary ammonium ions was reported among blood donors and atopic patients from Norway but not Sweden [15]. The only difference in environmental chemicals exposure was the use of cough syrups containing pholcodine available only in Norway. Subsequently, a marked increase in serum IgE antibodies to pholcodine, morphine and suxamethonium was demonstrated following pholcodine exposure in two sensitized individuals without a previous history of perioperative anaphylaxis [16]. This was also demonstrated in 11 individuals with a history of NMBA-induced anaphylaxis [17]. Both studies were conducted with a single dose of pholcodine, equivalent to a third of the daily recommended dose, taken daily for 1 week. The authors suggested a 'polyclonal booster effect' of pholcodine in order to explain the increase in IgE levels [16,17]. More recently, a positive association between pholcodine consumption and a prevalence of IgE sensitization to morphine and pholcodine, but not to succinylcholine and quaternary ammonium ions, was demonstrated in a comparison of pholcodine consumption in nine countries [18]. The IgE levels of pholcodine, morphine, succinylcholine and quaternary ammonium ions were collected in sera from each center, either routine allergy laboratories or from patients referred for allergological assessment [18]. These authors suggest that the use of drugs containing pholcodine should be questioned, because of 'the potential risk for NMBA-induced anaphylaxis'. The pholcodine cough medicine was withdrawn from the market in Norway in March 2007 as a result of these findings [16,17]. This led to a significant decrease in levels of IgE antibodies to pholcodine, morphine and suxamethonium and the frequency of NMBA-suspected anaphylaxis [19]. The 'pholcodine hypothesis' concept arose following these reports, especially in Europe.

There are certain facts that are important to understand prior to accepting 'the pholcodine hypothesis'. An immediate allergic reaction cannot be solely defined on the basis of an increased level of total IgE [3], such as those observed following pholcodine exposure. In addition, serum IgE antibodies against pholcodine, morphine or suxamethonium are not predictive of a subsequent allergic reaction to NMBAs [15–17]. Thus, the quantification of IgE sensitization might simply reflect in-vitro cross-reactivity without clinical relevance [20]. Moreover, IgE sensitization to pholcodine and morphine is prevalent even in low pholcodine-consuming countries, such as USA and the Netherlands. Therefore, IgE sensitization to pholcodine may occur even in the absence of pholcodine. The authors agree that these findings do not fit with the 'pholcodine hypothesis' and suggest that other environmental factors may lead to the production of IgE antibodies to pholcodine and suxamethonium [18]. In conclusion, the 'pholcodine hypothesis' may be an in-vitro phenomenon, because no relationship has been demonstrated between the prevalence of IgE sensitization to pholcodine, suxamethonium and/or morphine and the occurrence of NMBA-induced anaphylaxis.

Antibiotics

Perioperative anaphylaxis induced by antibiotics primarily involves penicillin and cephalosporins. Cross-reactivity between these families is lower than the often quoted 8–10% and is attributed to their common β-lactam ring and to the attached side chains attached [20]. First-generation cephalosporins and cefamandole share a similar structural side chain with penicillin and amoxicillin. Thus, patients allergic to penicillin or amoxicillin have a higher incidence of allergic reactions to first-generation cephalosporins and cefamandole but not to second-generation or third-generation cephalosporins [6••].

Food allergies and propofol

Current evidence suggests that egg-allergic, soy-allergic or peanut-allergic patients are not more likely to develop anaphylaxis when exposed to propofol.

Egg allergy and propofol

Egg allergy is most common during childhood and is usually outgrown by adulthood [21]. Five major allergens, *Gal d 1–5*, have been characterized in hen's egg [22]. Ovomucoid (*Gal d 1*) and ovalbumin (*Gal d 2*) originate primarily from the egg white and constitute 10 and 50% of white proteins, respectively. Chicken serum albumin (*Gal d 5*) is the major allergen in egg yolk [21].

Propofol is an alkylphenol derivative (2,6-di-isopropylphenol) marketed as an oil water emulsion using soybean oil (10%), and egg lecithin (1.2%) as the emulsifying agent. Lecithin (from the Greek lekithos, meaning egg yolk) is a highly purified phosphatide found in egg yolk, which is not the allergenic determinant [23]. The few documented IgE-mediated anaphylactic reactions to propofol have been shown to be elicited by the iso-propyl or phenol groups rather than the lipid vehicle [24,25]. Accordingly, prick tests with propofol and egg lecithin (egg phosphatide batch no. 120482, AstraZeneca, Caponago, Italy) were negative in 10 children with documented egg allergy (unpublished data). Even though two cases of anaphylaxis were recently 'attributed to propofol' in atopic children with multiple food allergies [26,27], skin testing was not performed leaving the diagnosis

presumptive. However, by reviewing both clinical scenarios, anaphylaxis may be ruled out in one case [26], and uncontrolled underlying asthma, as well as latex anaphylaxis, might have been involved in the second [27].

In conclusion, there is no confirmed report of propofol-induced anaphylaxis by allergy testing, in egg-allergic patients. Egg-allergic patients generally demonstrate immediate hypersensitivity to proteins from egg whites whereas lecithin is from the yolk egg. There is no reason to contraindicate propofol in egg-allergic patients.

Soy allergy, peanut allergy and propofol

In addition to the active component, the formulation of propofol also contains soybean oil. Soy allergy is one of the most common food allergies in childhood, affecting approximately 0.4% of children during the preschool years. It is considered an early-onset food allergy with most patients developing soy tolerance by late childhood [28]. Occasionally, soy allergy is present during adulthood. Refined soy oil, such as that present in propofol, is safe for people with soy allergy because the allergenic proteins are removed during the refining process. Thus, it is unlikely that the soy oil present in propofol may induce allergy, as the dose of protein contained in refined soy oil is too small to provoke a reaction [29]. Skin prick tests with propofol and soybean oil (purified soybean oil batch no. 10CB9982, AstraZeneca, Caponago, Italy) were negative in three patients with documented soy allergy (unpublished data). Therefore, there is no reason to contraindicate propofol in soy-allergic patients.

The potential for peanut-allergic patients to be sensitive to propofol is due to the fact that cross-reactivity occurs between soy and peanut, both being leguminous plants. Therefore, there are no data to support the avoidance of propofol in patients with peanut allergy.

Seafood allergies and iodinated drugs

There is no cross-reactivity between iodinated contrast agents, povidone iodine or seafood, as the allergenic determinant is not iodine for any of them. Therefore, the concept of 'iodine allergy' should be abandoned.

Seafood

The most important seafood groupings include the fish, crustaceans and molluscs. Crustaceans and molluscs are generally referred to as shellfish. Shellfish and fish are among the most common foods provoking severe anaphylaxis [30••]. Although the major allergens responsible for crustaceans-related anaphylaxis are tropomyosins, a heat-stable muscle protein, the major allergen in fish is the muscle protein parvalbumin. Shellfish allergens do not cross-react with fish allergens. Because the allergenic determinants for shellfish and fish are muscle proteins and not other components such as iodine, there is no reason to modify the anesthetic protocol in cases of shellfish-allergic or fish-allergic patients.

Povidone iodine

Povidone iodine is a stable iodophor solution containing a water-soluble complex of iodine and polyvinylpyrrolidone (PVP). PVP is a water-soluble polymer made from the monomer N-vinylpyrrolidone, which has been identified as the allergenic determinant by skin testing and immunoassays [31]. Less than 10 documented IgE-mediated allergic reactions have been reported following povidone iodine. Clinical features of these reactions are moderate and observed following topical, vaginal or rectal applications. The allergenic determinant of povidone iodine in cases of immediate hypersensitivity is povidone. There are no data to support potential cross-reactivity between shellfish and povidone iodine. Therefore, the only contraindication to povidone iodine is a previous documented hypersensitivity reaction to this antiseptic.

Iodinated contrast agents

All the currently available iodinated contrast media (ICM) are chemical modifications of a 2,4,6-tri-iodinated benzene ring [32•]. Although the allergenic determinant remains unknown, it is not the iodine atom. Cross-reactivity among the different ICM seems to be low despite their closely related molecular structures, but should be assessed through skin tests in order to identify safe alternative regimens [32•]. Patients with a previous documented IgE-mediated hypersensitivity to an ICM have been safely injected during subsequent radiological procedures with another ICM that was negative by skin testing [33]. In addition, there is no role to contraindicate the use of povidone iodine in patients allergic to ICM.

Fish allergy and protamine

Protamine sulfate is a strongly alkaline polypeptide that is used to reverse the anticoagulant effects of heparin. It can also be part of a complex with insulin, to delay its absorption and prolong its pharmacologic effect (e.g., neutral protamine Hagedorn or NPH). Protamine is produced from sperm or mature testis from salmon or related species. Even though up to 70% of patients who have undergone vasectomies develop antibodies to sperm antigens and a third develops auto-antibodies to protamine, no clinical reactions to protamine have been reported in patients with fish allergies or with prior vasectomies [34]. In addition, no cross-reactivity has been detected between salmon and protamine in sera from patients who had experienced anaphylactic reactions

upon ingestion of salmon [35]. In summary, IgE-mediated hypersensitivity to protamine is rare, and there is no reason to contraindicate the use of protamine in patients allergic to fish or with a prior vasectomy.

Treatment of anaphylaxis and allergological assessment

The severity and degree of systemic involvement and particularly severe cardiovascular homeostasis disturbances dictate the treatment options during anaphylaxis. Titrated epinephrine, as well as vascular loading, is the treatment of choice [2•]. The etiological diagnosis of an immediate reaction occurring during anesthesia relies on a triad including clinical, biological and allergological evidence. Clinical history and symptoms occurring during the immediate reaction should be recorded. Elevation of serum tryptase within 1–2 h of the anaphylactic episode is an indicator of a true IgE-mediated mast cell event. Skin testing should be done by experienced allergists to identify the pathophysiological mechanism of the reaction and the culprit allergen in order to provide safe alternative regimens [2•,3–5,6••].

Conclusion

There are many false assumptions about drug allergies, mostly based on anecdotal results. The concepts of multiple drug allergies and cross-reactivity between food and drugs are often quoted but not supported by the literature. For example, there is no contraindication to the use of propofol in patients allergic to eggs, soybean oil or peanuts. In addition, there are no data that support potential cross-reactivities between NMBAs and pholcodine or between protamine and fish. On the contrary, there are certain medications that do have cross-reactivity including NMBAs, iodinated contrast agents, penicillin and first-generation cephalosporins. Therefore, an allergy investigation should be done following an immediate hypersensitivity reaction with any of these medications in order to document a safe alternative regimen. Perioperative anaphylaxis may occur during the first or subsequent anesthetics, and the main risk factor is a previous immediate perioperative hypersensitivity reaction.

Acknowledgement

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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