

Editorial

Food, fads, allergies and anaphylaxis with propofol

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A food allergy is “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food” [1]. The prevalence of food allergy seems to have increased over the past few decades with rates of up to 10% reported in developed nations [2]. Consequently, children presenting for anaesthesia may also be reported to have food allergy, which may or may not be medically diagnosed. Common food allergens include the peanut, tree nuts, fish, shellfish, egg, milk, wheat, soy and seeds. The prevalence of these food allergies in children remains uncertain due to allergy definition, severity of reaction differences, study population characteristics and a focus on specific foods. Sommerfield et al. [3] have looked at the prevalence of food allergies in children presenting to a children's teaching hospital in Perth, Western Australia. Twenty-four of 1001 children reported egg and/or peanut allergy. However, only three children (0.3%) had evidence of likely IgE-mediated drug allergy. Diagnosis of a food allergy is usually initially considered due to clinical history, but history alone is not sufficient for diagnosis and may be influenced by perceived food intolerances and fads.

This is problematic for the anaesthetist managing children because some true food allergies can manifest with an allergic response to drugs commonly used in anaesthesia. Furthermore, allergenic cross-reactivity may be a feature of the immunoglobulin-E (IgE) response. Two allergens with common or similar epitopes can be recognised by a single antibody so sensitisation to one allergen can cross-sensitise a patient to the other without direct exposure [4]. Some clinicians avoid propofol in patients with egg, soy or peanut allergies out of concern that

there may be potential for the drug to contain enough allergen to trigger peri-operative anaphylactic reactions, although cross-reactivity is unlikely. Sommerfield et al. [5] report their exploration of the relationship between propofol and food allergies relating to egg, soy and peanuts in children in this issue of *Anaesthesia*. The issue is complex and their practice review goes some way to unravelling those complexities, allaying fears of an interaction.

The crux of the matter is whether children with allergy to egg, soy or peanut are at risk of allergy due to egg lecithin or soy oil as ingredients in propofol. Most children with egg allergy are sensitised to ovalbumin in egg white rather than lecithin in egg yolk. Soybean oil is regarded with caution in case it contains residual soy protein, or potential contamination with peanut allergen [6], with some patients with soybean allergy also having allergy to peanuts, which are both legumes. Food allergy diagnosis is usually based on history given by a parent or care giver. Although the history remains central to diagnosis it must be interrogated appropriately. Atopic children may be tested for sensitisation to allergens, including to eggs, without a history of clinical allergy. Food challenge remains the gold standard for diagnosis of food allergy [7], but may not be pursued for diagnosis where there is a clear history of food allergic reaction confirmed by specific allergy tests, or where allergy tests are such that allergy is highly likely. Sommerfield and colleagues [5] describe patients with sensitisation to egg, soy and peanut (i.e. the presence of specific IgE on allergy tests), a subset of whom were regarded as high-risk for allergy with recent allergy test results exceeding 95% positive prediction values for food allergic reaction. These children are those

who were treated with propofol and we can assume that these were children with true allergy.

Allergy vs. sensitivity

Parents and clinicians are very aware of children with peanut allergy who have suffered life-threatening events after minute exposure to that allergen. However, there is often confusion between what constitutes food allergy, sensitivity and intolerance. Food allergy is a reproducible adverse effect that has an underlying immunological mechanism after exposure to a specific food. Egg allergy occurs in about 2% of children, soy allergy in less than 1% of children and many of these children develop tolerance through exposure by the age of 5 years [2]. The development of tolerance to peanuts is less common and so, quite rightly, remains a concern even in later childhood. Food allergies to seeds, fish and shellfish are also considered persistent [2]. Efforts to reduce the incidence of allergies in children and to promote tolerance involve early introduction of allergens such as the peanut. These measures have been advised as a public health measure [2].

Somerfield et al. [5] conducted a retrospective 10-year review of children with a known positive skin prick test or elevated IgE concentrations to egg, soy, peanut or legumes, who were given propofol. Propofol datasheets warn about soy and egg allergy, and some also warn about peanut allergy in both Australia and New Zealand (e.g. Propofol-Lipuro, B. Braun Australia Pty. Ltd., NSW, Australia, and Fresofol, Fresenius Kabi Australia Pty. Ltd., NSW, Australia). The authors were able to identify 304 children with known true food allergies who had been given propofol as part of their anaesthetic care. Only one likely mild allergic reaction was experienced by a child with a previous history of intralipid allergy. These children were not denied the benefits of propofol despite package warnings of allergic reactions, suggesting that many paediatric anaesthetists consider the association baseless; an opinion supported by other limited reviews that have failed to demonstrate an increased risk of allergic reaction to propofol in egg-allergic patients [8–12].

Specific examples

Children with egg allergy have received measles–mumps–rubella vaccine (containing traces of ovalbumin), with the vaccine viruses grown in chicken embryo fibroblasts, without untoward experience [13–15]. Propofol is an alkylphenol derivative (2,6-di-isopropylphenol) formulated as an oil-in-water emulsion using 10% refined soybean oil, 1.2% highly purified egg lecithin and 2.25% glycerol. Hen (*Gallus domesticus*) egg lecithin has not been reported to

trigger allergic reactions although two of nine proteins present (Gal d 5 and Gal d 6) are possibly immunogenic. Although propofol is a soy-based emulsion, protein moieties are removed during the manufacturing process rendering the soy oil exceedingly unlikely to trigger an immunologically based anaphylactic reaction. Peanut allergy is raised as a concern for propofol use due to potential clinical cross-reactivity between peanut and soy, both belonging to the legume family, with approximately 5% cross-reactivity between soy and peanut allergy [16]. However, the likelihood of an allergic reaction is exceedingly low if there is no allergenic protein in the propofol, and in addition most peanut allergic patients are clinically tolerant of soy. There is little evidence for the practice of choosing alternatives to propofol in patients with egg, peanut or soy allergy [11] and Sommerfield et al. [5] are quite justified to continue their practice of administering propofol in the presence of food allergy.

Some medications do exhibit cross-reactivity (e.g. penicillin and first-generation cephalosporins, neuromuscular blocking drugs and iodinated contrast agents). Evidence for food allergies that can cause allergic reactions in the presence of drugs used in anaesthesia is less common. Food allergies may be problematic for some drugs (e.g. alpha-gal syndrome, an IgE-mediated red meat allergy and gelatin-based colloid) [2], although many of these reported relationships have scant supportive data, for example, fish or shellfish allergy and iodine, fish and protamine, neuromuscular blocking drugs and pholcodine (morpholinylethylmorphine) [17]. The supposition that genuine serious allergic reaction to propofol is rare and is not reliably predicted by a history of food allergy in children is a conclusion reached by others [11]. Most agree that it is not an issue in adults [18].

Another food allergy is associated with latex. About half of those with latex allergy can react to fruits such as avocado, banana, kiwifruit, passionfruit, plum, strawberry and tomato (latex-fruit syndrome). Allergen cross-reactivity is due to IgE antibodies that recognise structurally similar epitopes on different proteins that are phylogenetically closely related or represent evolutionarily conserved structures. For example, class-1 chitinases containing an N-terminal hevein-like domain cross-react with hevein, a major IgE-binding allergen for patients allergic to latex. However, it is uncertain if latex sensitisation precedes or follows the onset of food allergy.[19] Naturally, this cross-reactivity is a concern but most medical centres are moving away from equipment containing natural latex rubber.

Anaphylactic reactions to propofol certainly occur, but are possibly more related to the phenyl nucleus and the

isopropyl groups or ethylenediaminetetraacetic acid (EDTA) contained in the formulation [17]. The incidence of allergic reactions to propofol in children remains uncertain. Clinical features suggesting allergy in children undergoing anaesthesia may include hypotension, wheeze with tracheal intubation or skin rash, with supporting evidence possible from skin tests, measurement of mast cell tryptase and specific IgE concentrations.[20] Symptoms and signs can be attributed to causes other than anaphylaxis. The classification of peri-operative anaphylaxis is evolving and a new structured method for classifying suspected anaphylactic events including the degree of certainty with which a causal trigger agent can be attributed was used in the sixth National Audit Project (NAP6) [21]. Antibiotics and neuromuscular blocking drugs featured highly in the NAP6 study, and only one patient reacted adversely to propofol [22]. If the true incidence is very small, then the current study involving 304 children with assorted food allergies who suffered no consequences after anaesthesia induction is not enough to make a definitive statement. If a 2% incidence of allergy is assumed, then the denominator in NAP6 would have been 2% of 2.4 million, that is, 1: 48,000 children. This current study [5] is simply supportive of such a statement, given an improved understanding of the nature of food allergies, denatured constituents of propofol and alternative triggers causing symptoms after propofol administration.

There may be conditions that deserve greater scrutiny. Eosinophilic oesophagitis is a condition characterised by oesophageal dysfunction and eosinophil-predominant inflammation. It is frequently associated with IgE-mediated food allergy [10]. Patients with eosinophilic esophagitis undergo numerous anaesthetics for diagnostic and surveillance endoscopy. However, even in this situation, propofol is likely to be safe in egg-allergic children without prior egg anaphylaxis.

Food allergies are frequently volunteered by parents of children presenting for anaesthesia. Information about food allergies is sought during pre-operative assessment. Health professionals quite rightly encourage the use food allergy 'alarm bracelets' in both the community and in hospital where exposure to specific allergens can be life-threatening. However, concerns about food allergies and reactions to common anaesthesia drugs appear less grounded than thought 10 years ago. Some might advocate that it is somewhat silly to have multiple food allergies and intolerances, true or untrue, to be recorded on wristbands, anaesthesia notes and in Anaesthesia Information Management Systems. That attitude ignores the role of the anaesthetist as a peri-operative physician;

children may be exposed to food allergens at any time during their hospital stay and information concerning this important matter should be freely available.

The American Academy of Allergy, Asthma and Immunology recently stated that egg- or soy-allergic patients can receive propofol without any special precautions [23]. The current study from Sommerfield et al. [5] adds further support for this statement. The main risk factor for a peri-operative anaphylactic event in children, as in adults, is a history of a previous immediate peri-operative reaction and not a history of a food allergy.

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