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¹ Ehrenfeld et al. *J Blood Disorders Transf*. 2014; 5:9. ² Awada WN et al. *J Clin Monit Comput*. DOI 10.1007/s10877-015-9660-4. *Study Protocol: In each group, if researchers noted SpHb trended downward below 10 g/dL, a red blood cell transfusion was started and continued until SpHb trended upward above 10 g/dL. The transfusion threshold of 10 g/dL was predetermined by the study protocol and may not be appropriate for all patients. Blood sampling was the same for the control and test group. Arterial blood was drawn from a 20 gauge radial artery cannula into 2 mL EDTA collection tubes, mixed and sent for analysis by a Coulter GEN-S Hematology Analyser.

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Original Article

Propofol use in children with allergies to egg, peanut, soybean or other legumes*

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Summary

Propofol is the most commonly administered intravenous agent for anaesthesia in children. However, there are concerns that the emulsified preparation may not be safe in children with an allergy to egg, peanut, soybean or other legumes. We conducted a retrospective study of children with immunologically confirmed egg, peanut, soybean or legume allergy and who underwent general anaesthesia at Princess Margaret Hospital for Children between 2005 and 2015. We extracted details regarding allergy diagnosis, each anaesthetic administered and any adverse events or signs of an allergic reaction in the peri-operative period. A convenience sample of patients without any known food allergies was identified from our prospective anaesthesia research database and acted as a control group. We identified 304 food-allergic children and 649 procedures where propofol was administered. Of these, 201 (66%) had an egg allergy, 226 (74%) had a peanut allergy, 28 (9%) had a soybean allergy and 12 (4%) had a legume allergy. These were compared with 892 allergy-free patients who were exposed to propofol. In 10 (3%) allergy patients and 124 (14%) allergy-free patients, criteria for a possible allergic reaction were met. In nine of the food-allergic children and in all the controls valid non-allergic explanations for the clinical symptoms were found. One likely mild allergic reaction was experienced by a child with a previous history of intralipid allergy. We conclude that genuine serious allergic reaction to propofol is rare and is not reliably predicted by a history of food allergy.

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Introduction

Food allergies are increasingly common worldwide, which raises concerns regarding allergic reactions to medications that contain food proteins [1]. Propofol is the most common intravenous (i.v.) agent used for the induction and maintenance of anaesthesia and is formulated in a lipid

emulsion (intralipid) which contains egg lecithin and soybean oil. Anaphylactic reactions to propofol occur at a rate of one in 60,000 adults [2]. There have been several cases described that suggest a link to egg or peanut allergy [3, 4].

Consumer medicine information leaflets for Propofol-Lipuro (B. Braun Australia Pty. Ltd., NSW, Australia), Fresofol

(Fresenius Kabi Australia Pty. Ltd., NSW, Australia), Propofol Sandoz (Sandoz Pty. Ltd., NSW, Australia), Provive (AFT Pharmaceuticals Pty., NSW, Australia) and Diprivan (Aspen Pharmacare Australia Pty. Ltd., NSW, Australia) warn against use in patients with allergies to emulsion components, including egg lecithin and soybean oil. Labels on Propofol-Lipuro and Fresofol also warn against use in patients with peanut allergy because cross reactions between soybean and peanut allergens (both legumes) occur in a third of allergy sufferers [5] and soybean oil may also be contaminated with residual peanut allergen during manufacture [6].

Several small retrospective studies that included 308 patients, of which 83 were children, have failed to demonstrate an increased risk of allergic reaction to propofol in egg-allergic patients [7–11]. To our knowledge there have been no studies which have investigated whether children with peanut and legume allergies are at increased risk of propofol allergy.

We decided to conduct a retrospective study in order to assess the safety of propofol in children with egg, peanut, soybean or legume allergy, or sensitivity, in a larger cohort than previously examined. We also compared the rates of potential allergic reaction in food-allergic children with those in children without food allergies.

Methods

This study was conducted at Princess Margaret Hospital for Children (now Perth Children's Hospital), Perth, WA, Australia, and was approved by our hospital's Institutional Ethical Committee and registered with the University of Western Australia's Human Research Ethical Committee. Participants with an allergy or sensitisation to egg, peanut, soybean or legumes were identified from a Department of Clinical Immunology database which contained patient data from 2005 to 2015. We cross-referenced these records with the Theatre Management System in order to identify patients who had also undergone general anaesthesia. Anaesthesia and recovery area records, as well as medical notes for each potential participant, were reviewed for baseline characteristics, administration of propofol, opioids, antibiotics, steroids, antihistamines and other agents, and for any evidence of potential allergic reactions. The nature of the reaction was recorded as respiratory (cough, wheeze, stridor); cutaneous (rash, swelling, pruritus, flushing, angioedema); cardiovascular (hypotension, tachycardia, cardiac arrhythmias, cardiovascular collapse); or gastrointestinal (abdominal cramps, diarrhoea). Immunology records were reviewed for date of initial immunological assessment, allergy diagnosis, nature of any allergic

reaction, and details of a skin prick test and serum-specific IgE results. Clinical allergy was defined as symptoms or signs of allergy after exposure to a food allergen with the diagnosis confirmed by a clinical immunologist. We considered allergic sensitisation to be present when any skin prick test was positive (with a wheal that was at least 3 mm larger than control) or IgE levels above 0.35 kU.ml^{-1} , independent of symptoms. We considered children who had serum IgE above 6 kU.ml^{-1} for egg white or above 15 kU.ml^{-1} for peanut in the 12 months before a propofol exposure to have a high risk for food allergy, as these cut-offs are associated with reactivity on exposure to egg and peanut, respectively, in 95% of cases [12]. Potential allergic reactions were reviewed by two anaesthetists (DS and BvU-S) and a clinical immunologist (ML) in order to confirm or refute allergy. We also selected a convenience sample of patients with similar age and sex distribution without known food allergies who underwent general anaesthesia from our database of prospective anaesthesia research participants as a control group.

Case details were entered into a database created for the study. Control records were collated using Microsoft Excel (Microsoft Corporation, CA, USA). Statistical analysis consisted of descriptive statistics and was performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) [13] and RStudio version 1.1.456 (RStudio Inc., Boston, MA, USA) [14].

Results

We identified 2608 children with a relevant clinical food allergy or sensitivity, comprising 1091 (41.8%) to egg, 1354 (51.9%) to peanut, 40 (1.5%) to soybean and 123 (4.7%) to other legumes. Of these, 383 children received a general anaesthetic, with 304 exposed to propofol and therefore included in the study (Fig. 1). Baseline characteristics of these 304 children together with those of the control group of 892 children are shown in Table 1. The cohort included 211 (69.4%) male patients and 93 (30.6%) female patients. The 304 children underwent a total of 646 procedures with propofol exposure; 186 (61.2%) children had one procedure, 95 (31.3%) had two to five procedures and 23 (7.6%) had six or more procedures over the course of our study period. In 376 (58.2%) cases, i.v. propofol was used for induction or co-induction of anaesthesia only. The 304 patients between them had a total of 637 allergies to egg, peanut, soybean or legume (Table 2). Patients with two co-existing allergies are shown in Table 3. Atopic disease was reported in 243 (79.9%) children.

There were 191 (29.6%) procedures which occurred within one year of a positive skin prick test or IgE result. In

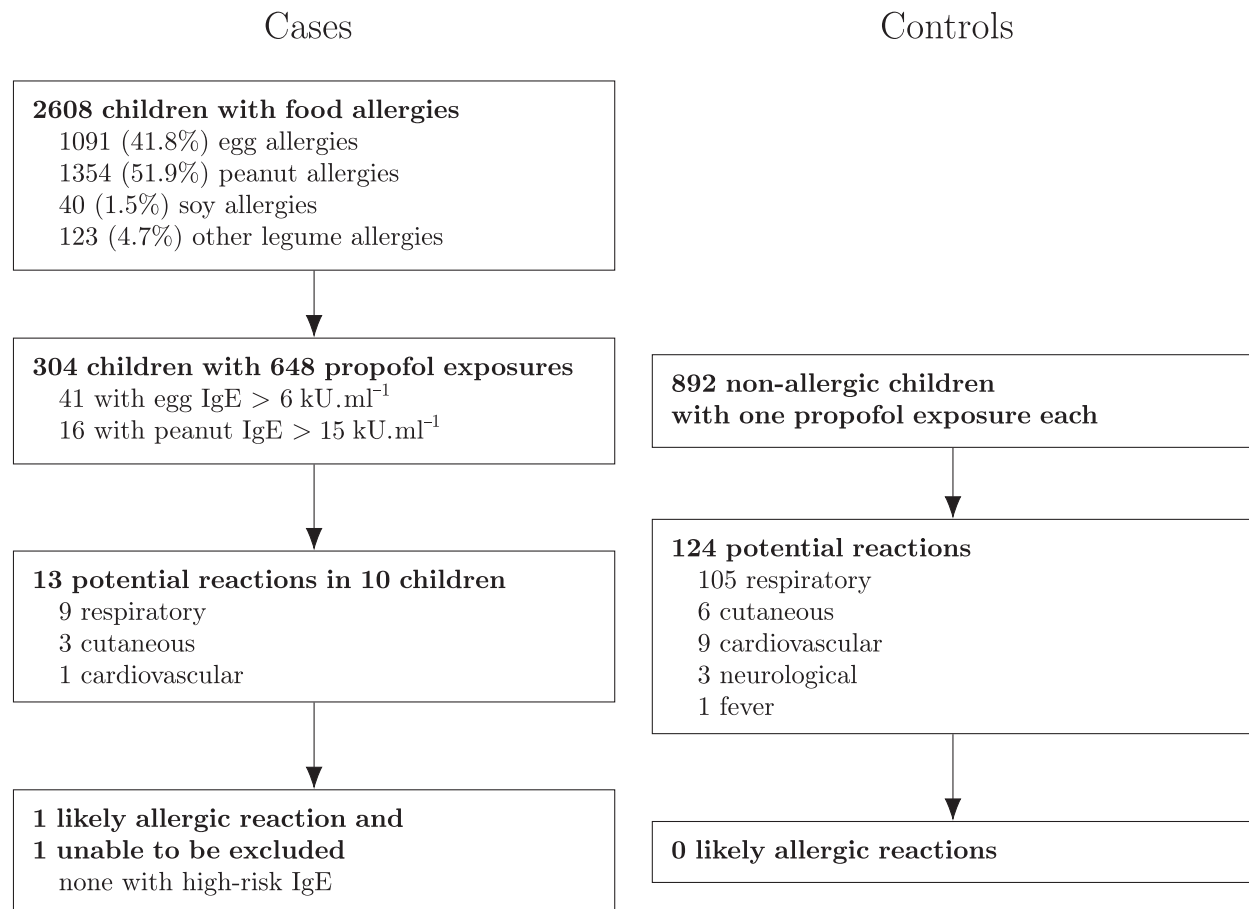


Figure 1 Flow diagram showing the allergy cases group and non-allergy control group included in the review.

egg-allergic children, 102 (25.4%) of 402 procedures occurred within one year of a positive result, as did 139 (27.8%) of 500 procedures in peanut-allergic children, 16 (17.4%) of 92 procedures in soybean-allergic children and 5 (17.9%) of 28 procedures in legume-allergic children. There were 21 children with high-risk IgE levels who received 26 propofol exposures (12 with egg white IgE > 6 kU.ml⁻¹, 16 with peanut IgE > 15 kU.ml⁻¹, including two with both).

Allergies known to be diagnosed before a procedure were noted on the anaesthetic records in 113 (57.9%) of 195 cases for egg, in 104 (48.4%) of 215 cases for peanut, in 9 (23.7%) of 38 cases for soybean, and in 7 (70.0%) of 10 cases for legumes. In addition, allergies only later formally diagnosed were reported in 21 (33.3%) of 63 cases for egg, 29 (33.7%) of 86 cases for peanut, 0 (0.0%) of 12 cases for soybean and in 1 (33.3%) of 3 cases for legumes. There were 68 procedures with propofol exposure in 42 patients documented as having outgrown their egg allergy, 22 procedures in 15 patients who had outgrown peanut

allergy, and one procedure in a patient who had outgrown soybean allergy.

In 10 patients, after propofol administration, criteria for a possible allergic reaction were met (Table 4). Reported features were respiratory (wheeze or cough) in nine, swelling in one, rash in two and cardiovascular in one. Except for two cases, non-allergic explanations for the clinical features were determined to be more likely. No major cardiorespiratory compromise occurred and no treatment with adrenalin was required in any of the patients.

The first case was a 4-year-old egg-allergic male with short gut syndrome who had been receiving total parental nutrition (TPN) infusions. Peri-orbital and peri-oral swelling was noted two hours after his 10th propofol exposure (20 mg administered as part of induction of anaesthesia), without tongue oedema, respiratory or cardiovascular compromise, and he responded to treatment with hydrocortisone and promethazine. Similar symptoms had

Table 1 Baseline patient characteristics of allergic and non-allergic control patients exposed to propofol and included in the study. Values are median (IQR [range]) or number (proportion).

	Allergic group n = 304	Control group n = 892
Age; years	5.0 (2.7 – 8.8 [0.0 – 18.0])	6.0 (3.9 – 9.6 [0.0 – 17.0])
Weight; kg	18.6 (13.6 – 28.3 [3.1 – 88.7])	22.5 (16.5 – 36.3 [2.3 – 121.0])
ASA physical status		
1	183 (28.2%)	524 (58.7%)
2	298 (46.0%)	351 (39.3%)
3	163 (25.2%)	16 (1.8%)
4	4 (0.6%)	0
Total propofol dose; mg	80 (40 – 140 [4 – 1442])	50 (30 – 140 [4 – 2250])
Total propofol per kg body weight; mg.kg ⁻¹	4.0 (2.4 – 5.4 [0.4 – 40.0])	2.4 (1.3 – 4.3 [0.2 – 29.9])
Anaesthesia duration; min	39 (24 – 64 [8 – 322])	47 (33 – 68 [6 – 1424])
Recovery area duration; min	35 (28 – 45 [11 – 166])	40 (31 – 52 [11 – 1408])

Table 2 Propofol-exposed children allergic to egg, peanut, soybean or other legumes, who had documented positive IgE, documented positive skin prick test (SPT) or documented clinical features of allergy. Values are number (proportion).

Allergen	n	Positive IgE	Positive SPT	Clinical allergy
Egg	201 (66.1%)	108 (35.5%)	178 (58.6%)	169 (55.6%)
Egg white	192 (63.2%)	108 (35.5%)	175 (57.6%)	161 (53.0%)
Egg yolk	160 (52.6%)	23 (7.6%)	139 (45.7%)	135 (44.4%)
Unidentified ^a	9 (3.0%)	1 (0.3%)	3 (1.0%)	7 (2.3%)
Peanut	226 (74.3%)	145 (47.7%)	202 (66.4%)	160 (52.6%)
Soybean	28 (9.2%)	17 (5.6%)	14 (4.6%)	13 (4.3%)
Legume	12 (3.9%)	7 (2.3%)	7 (2.3%)	10 (3.3%)

^aA clinical immunologist had diagnosed an egg allergy, but it could not be determined from available records if the allergen was egg white or egg yolk.

Table 3 The number of children with two or more allergies (n = 194). Values are number (proportion).

Allergen	Egg	Peanut	Soybean	Legume
Egg	–	126 (41.4%)	20 (6.5%)	8 (2.6%)
Peanut	126 (41.4%)	–	24 (7.9%)	9 (3.0%)
Soybean	20 (6.5%)	24 (7.9%)	–	7 (2.3%)
Legume	8 (2.6%)	9 (3.0%)	7 (2.3%)	–

been noted previously when intralipid was included in his TPN infusions, requiring antihistamine cover. The night before surgery he had received intralipid under antihistamine cover, resulting in minor facial swelling that had resolved before arrival in theatre. Subsequent testing revealed an egg white-specific low positive IgE of 0.093 kU.l⁻¹, and positive SPT for egg white and egg yolk. Skin testing with propofol drug moiety was not performed.

His clinical features were thought to be triggered by the combination of intralipid exposure the night before and the propofol exposure during anaesthesia.

The second case was an asthmatic 8-year-old male with known allergies to eggs, nuts, seafood and grasses who had received one previous uneventful propofol exposure. Shortly after arrival in the recovery area he felt short of breath and oxygen saturation decreased to 85% breathing room air. He responded to nebulised salbutamol 5 mg, sitting up and CPAP. The clinical impression was atelectasis and mild bronchospasm, although allergic reaction to propofol cannot be excluded.

We included 892 controls with no reported allergies who underwent a procedure with propofol administration (Table 1). Possible allergic symptoms or signs were identified in 124 procedures (105 respiratory, 9 cardiovascular, 6 cutaneous, 3 neurological, 1 fever). One child with a hive on their eyelid, intra-operative wheeze and

Table 4 Summary of diagnosed allergy, medical history, nature of suspected reaction and clinical impression in ten patients with possible reactions following propofol exposure.

Case	Allergy	Other allergies, atopy	Background medical information	ASA physical status	Reaction sign	Treatment	Possible cause
#1	Egg white Egg yolk	EMLA, dressing, hayfever	GEFS+, SCN1 Mutation, PEG fed, rhinoconjunctivitis	3	Tachycardia	–	Sepsis
#2	Egg white Egg yolk Peanut	Tegaderm dressing	Wiskott–Aldrich Syndrome	2	Stridor	–	Stridor after every tracheal intubation
#3	Egg white Peanut	Cefaclor, shellfish,	Asthma, rhinoconjunctivitis	2	Mild audible wheeze without oxygen desaturation	–	Asthma, current upper respiratory infection, wheeze directly after tracheal extubation
#4	Egg white	–	Juvenile myelomonocytic leukaemia	3	Generalised skin rash	Promethazine 7.5 mg	Platelet infusion reaction
	Egg yolk			3	Cough	–	Tolerated propofol without any adverse event in five following procedures
#5	Peanut	Ceftazidime	CF, asthma, eczema, rhinoconjunctivitis, MBL deficiency	3	3 × cough	CPAP	After CT scan + bronchoscopy
#6	Egg white Egg yolk	Mosquito bite	OSA, asthma, syringomyelia, MBL deficiency	3	Cough	4 mg Dexamethasone 10 mg Loratadine postop	After two tracheal intubation attempts
#7	Egg white Egg yolk Peanut	Fentanyl, oxycodone, tapes, cow's milk, chicken, kiwi fruit	VACTERL syndrome premature, single right dysplastic kidney, eczema	3	Localised skin rash on operation side	–	Reaction to Betadine
#8	Egg white Egg yolk	–	OSA	2	Brief oxygen desaturation to 85%	CPAP	OSA
Possible reaction cases							
#9	Egg white Egg yolk	–	Born at 28 weeks gestation, chronic lung disease, bronchomalacia, gastroschisis, short gut syndrome, PEG & TPN-fed	3	Facial swelling (peri-oral and peri-orbital)	60 mg Hydrocortisone 3 mg Promethazine	Likely intralipid reaction given previous history of facial swelling with TPN
#10	Egg white Egg yolk Peanut	White fish, grass	Asthma, rhinoconjunctivitis, eczema	2	Oxygen desaturation to 90%, wheeze	2 × 2.5 mg Ventolin, CPAP	Atelectasis and mild bronchospasm following extubation

EMLA: eutectic mixture of local anaesthetic; GEFS+: Genetic epilepsy with febrile seizures plus; CF: cystic fibrosis; MBL deficiency: Mannose-binding lectin deficiency; CPAP: Continuous Positive Airways Pressure; OSA: obstructive sleep apnoea; VACTERL: Vertebral anomalies, anal atresia, cardiac defect, tracheo-esophageal fistula, renal abnormalities, limb abnormalities; TPN: total parenteral nutrition.

pruritus in recovery received antihistamines postoperatively. No patient required follow-up for allergic symptoms and, on review, allergic reaction to propofol was considered unlikely to have caused any of the symptoms identified.

Discussion

In 304 patients with immunologically confirmed food allergy with 649 exposures to i.v. propofol, two patients had potentially allergic symptoms where propofol could

Table 5 Studies examining propofol use in potentially sensitised patients.

First author and year of publication	Study details	Number of patients reviewed, (patients with propofol) [propofol exposures]	Number of adverse events	Likely allergic reaction to propofol
Molina-Infante; 2013	Adults with EoE sensitised to egg, soybean or peanut	60 (52) [404]	1	No (SPT to propofol negative)
Asserhøj; 2016	Adults allergic to egg, soybean or peanut	99 [171]	17	No
Murphy; 2011	Children allergic to egg	42 (28) [43]	1	Yes (SPT to propofol 3 × 3 mm; treatment with adrenaline)
Mehta; 2016	Children with food allergy and EoE	68 without EoE [38] and 76 [27] with EoE	2	No
Wiskin; 2015	Children with food allergy undergoing endoscopy	131 (55) [76]	13	No
Our study	Children with allergies to egg, soybean, peanut and other legumes	383 (304) [649]	13	1 × yes 12 × no
	Children without food allergies	1664 (892) [892]	124	No

EoE: eosinophilic esophagitis; SPT, skin prick test.

not be excluded as the cause. This suggests that the rate of reaction to propofol may be higher in food-allergic children than the 1 in 60,000 seen in the general population [2]. As demonstrated by our control group however, mild adverse skin and respiratory reactions during, or immediately after, anaesthesia are common, usually self-limiting and can resemble allergic reactions. The single patient in our cohort with a likely reaction to intralipid had a mild-to-moderate reaction without significant compromise. There was little evidence to support a connection between allergy to egg, peanut, soybean or other legumes and risk of a serious allergic reaction to propofol. Coughing and other respiratory symptoms were the most frequent potential reactions identified but explanations other than propofol allergy were more likely in all cases except one. No patient was persistently hypotensive and none developed erythema or generalised urticaria. In the NAP6 study, peri-operative anaphylaxis was associated with hypotension in all cases [15].

There were many more potential reactions identified in our control group of patients without reported allergies. This is largely attributable to increased vigilance, as these patients were prospectively collected during studies examining adverse respiratory events and a high number of minor adverse respiratory events were noted. From this, we conclude that minor respiratory and skin reactions are common during anaesthesia and overlap significantly with

the typical signs of allergy, making it difficult to distinguish one from another.

There have been five (two adult and three paediatric) small observational cohort studies examining sensitised populations with similar findings to our study (Table 5). Murphy et al. [9] included 28 egg-allergic children based on a clinical history of allergy or highly positive SPT > 7 mm. They reported one patient with a history of egg anaphylaxis and other food allergies, including peanut and soybean sensitivity, who developed an allergic reaction with generalised erythema and urticaria within 15 min of propofol administration [9].

The food components in propofol may not be present in sufficient quantities to trigger an allergic reaction [16]. The threshold dose of oral soybean to trigger an allergic reaction is of the order of 300 µg protein [17]. The relatively small amount of soybean remaining after the refining process might be insufficient to trigger an allergic reaction, even in a sensitised individual, as it has been shown that only up to 0.32 µg.ml⁻¹ soybean remains in the refined oil [18]. The highest dose of 10% (v/v) soybean oil-containing propofol given in our study was 1442 mg, therefore, potentially 4.6 µg of soybean protein, with the median propofol dose (80 mg) containing 0.26 µg soybean protein.

The lowest dose triggering an allergic reaction to egg orally is 2 mg [18]. Propofol emulsion contains 1.2% (w/v) purified egg lecithin, with an egg protein contamination

rate of 0.005% [19]. The maximum propofol dose administered in this study contained 1730 mg egg lecithin exposing this patient to 87 µg egg protein. The median propofol dose in this study would contain 4.8 µg egg protein.

In addition, most egg-allergic patients react to proteins derived from egg white such as ovalbumin [20], whereas propofol contains egg lecithin, highly purified from the egg yolk. It is not known whether egg lecithin contains the two most common allergenic proteins found in egg yolk. Nine of our 160 egg yolk-allergic patients had a potential reaction after propofol administration but none were life-threatening. A report by Dewachter et al. testing 10 egg-allergic children showed negative SPT results to both propofol and egg lecithin; similarly, three soybean-allergic children tested negative for propofol and soybean oil [21]. The authors stated that the two case reports [3, 22] of propofol anaphylaxis in children with egg allergy were not confirmed by testing and inconclusive on history alone. In a Spanish adult study, skin testing with propofol and its lipid vehicle (intralipid) was negative in 25 patients with documented allergy to either egg, legumes or both [23]. Reassuringly, the measles and influenza vaccines, despite having trace amounts of ovalbumin, are considered safe to administer in children with an egg allergy [24], although it should be acknowledged that the amount of egg or soybean necessary to trigger a reaction intravenously might be different from the intramuscular route of administration.

In addition to potentially allergenic food components, there are two sensitising epitopes in propofol; the isopropyl side chain and phenyl group. These moieties are present in other drugs and cosmetics and may cause reactions on first exposure. One study tested 14 patients who reported a reaction after first exposure to propofol [8] and none had concurrent food allergies. The authors concluded that it was due to the isopropyl or phenyl group, rather than the intralipid emulsion, in these cases. This is also supported by other reports of patients without food allergies reacting to propofol [25–27]. Recently there have been cases of allergy to ethylenediamine tetra-acetic acid (EDTA), another excipient in propofol [28].

Our study was limited by a relatively small number of children allergic to soybean or other legumes. Due to the retrospective design, we assumed an allergy for every positive reaction on skin prick testing or IgE testing, which may not always equate with a clinical allergy. Furthermore, only 132 (43%) of 304 children were exposed to propofol within one year after positive testing, and some may have lost their clinical reactivity between testing and propofol exposure. Approximately 50–70% of those allergic to egg

[29] or soybean [30] eventually outgrow their allergy, but 77% of peanut-allergic children [31], representing nearly half our patients, never do. Dexamethasone 0.15 mg.kg⁻¹ was administered during 168 (26%) procedures (after initial propofol administration) for postoperative nausea and vomiting prophylaxis, but it is unlikely it would have masked an allergic reaction completely as steroids are not effective in the immediate management of anaphylaxis [32]. We excluded nausea and vomiting as a potential symptom of allergy because it is common after anaesthesia and would not have been useful as an anaphylaxis diagnostic criterion.

In the 10 cases where an adverse event was noted, one was deemed a probable allergy and in another propofol allergy could not be excluded. Patients were not tested further to determine whether the reaction was due to propofol sidechains or the food component. Overall, propofol was safely administered in children with allergies to egg, peanut, soybean or other legumes. In one child a likely allergic reaction occurred that was not severe and should, in retrospect, have been predictable with better history taking. Some of the classic features of mild allergic reactions are common during general anaesthesia and are often not useful for diagnostic purposes. We conclude that serious allergic reactions to propofol are rare and are not reliably predicted by a history of allergy to egg, peanut, soybean or other legumes.

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