Allergic Reactions to Propofol in Egg-Allergic Children

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**BACKGROUND:** Egg and/or soy allergy are often cited as contraindications to propofol administration. Our aim was to determine whether children with an immunoglobulin (IgE)-mediated egg and/or soy allergy had an allergic reaction after propofol use.

**METHODS:** We performed a retrospective case review over an 11-year period (1999–2010) of children with IgE-mediated egg and/or soy allergy who had propofol administered to them at the Children’s Hospital Westmead, Sydney.

**RESULTS:** Twenty-eight egg-allergic patients with 43 propofol administrations were identified. No child with a soy allergy who had propofol was identified. Twenty-one children (75%) were male, the median age at anesthesia was 2.4 years (range, 1–15 years), and the presence of other atopic disease was common (eczema 61%, asthma 32%, peanut allergy 43%). Most children (n = 19, 68%) had a history of an IgE-mediated clinical reaction to egg with evidence of a significantly positive egg white skin prick test (SPT) reaction (≥7 mm). Two of these had a history of egg anaphylaxis. The remaining children (n = 9, 32%) had never ingested egg because of significantly positive SPT (≥7 mm). All SPTs to egg were performed within 12 months of propofol administration. There was one nonanaphylactic immediate allergic reaction (n = 1 of 43, 2%) that occurred 15 minutes after propofol administration in a 7-year-old boy with a history of egg anaphylaxis and multiple other IgE-mediated food allergies (cow’s milk, nut, and sesame). SPT to propofol was positive at 3 mm. No other egg-allergic child reacted to propofol.

**CONCLUSIONS:** Despite current Australian labeling warnings, propofol was frequently administered to egg-allergic children. Propofol is likely to be safe in the majority of egg-allergic children who do not have a history of egg anaphylaxis. (Anesth Analg 2011;XX:●●●●●●●)

Propofol (2,6-diisopropylphenol) is a frequently used IV hypnotic drug for induction and maintenance of anesthesia. All propofol preparations with the exception of newly available fospropofol (Lusadera™; Eisai, Inc., Woodcliff Lake, NJ) are lipid suspensions that contain egg lecithin/phosphatide and soy oil. In Australia, a history of hypersensitivity to egg and soy are listed as contraindications in the manufacturer’s product information. Egg allergy is the most common immediate food allergy in Australian children, with an estimated incidence of up to 9%. This contraindication therefore has potential significant implications for many children.

Propofol hypersensitivity reactions are uncommon compared with those triggered by other hypnotic drugs or muscle relaxants. However, in the largest case series of 14 patients with propofol hypersensitivity, no mention is made regarding the presence of egg or soy allergy. There have only been 5 published cases of suspected allergic reactions after propofol administration in egg-allergic individuals. In all cases, the details of the patient’s egg allergy were unclear and no skin prick test (SPT) or intradermal test to the incriminating propofol preparation was performed.

There is still no agreement among physicians regarding propofol and patients with egg allergy, with some suggesting that egg-allergic patients are not more likely to develop anaphylaxis when exposed to propofol. The 2009 guidelines on suspected anaphylactic reactions associated with anesthesia published by the Association of Anesthetists of Great Britain and Ireland claim there is no evidence that propofol should be avoided in egg- or soy-allergic patients but suggest a cautious approach is required in such patients. The warning labels differ among countries for the same formulation of propofol supplied by the same company. The product information for Diprivan 1% warns of its use in egg- or soy-allergic individuals in Australia, soy/peanut (but not egg) in the United Kingdom, and lists no food allergy warnings in the United States. This is despite all 3 formulations being supplied by the same company (AstraZeneca Pty Ltd), and all containing soy oil and egg lecithin (United States and Australia) or egg yolk phosphatide (United Kingdom; egg yolk phosphatide containing egg lecithin).

There are no published data examining the rate of allergic reactions in a cohort of egg- or soy-allergic patients. The aim of this study was to investigate whether any child with documented immunoglobulin (IgE)-mediated egg and/or soy allergy had an allergic reaction after propofol administration.

**METHODS**

Approval was obtained from the Children’s Hospital at Westmead (CHW) Ethics Committee before reviewing patient records. Consent from patients or their guardians before reviewing the charts was not required.
A retrospective chart review of propofol administration to egg- and/or soy-allergic pediatric patients at the CHW, Sydney, for 1999 to 2010 was performed. Records were identified by 2 strategies: first, by a search through the Department of Allergy and Immunology database for patients with egg or soy allergy; second, by a word search through the department’s patient correspondence letters using the key phrases “egg/soy allergy,” “anaphylaxis,” and “avoidance of egg/soy.” All identified records were reviewed to determine whether the patients had ever undergone a procedure under an anesthetic at the hospital.

Patients were identified as having IgE-mediated egg allergy if they had either (1) evidence of IgE egg sensitization (i.e., SPT to egg white ≥7 mm or serum egg-specific IgE level of >7 kilounits antibody [kUA]/L) with or without a history of an immediate clinical egg-allergic reaction (i.e., after eating scrambled/boiled/baked egg), or (2) evidence of IgE egg sensitization (i.e., SPT to egg white 3–6 mm or serum egg-specific IgE level of >0.35 kUA/L and ≥7 kUA/L) with a history of an immediate egg-allergic reaction.

IgE-mediated soy allergy was defined as serum soy-specific IgE level of >30 kUA/L with or without a history of an allergic reaction to soy. Serum soy-specific IgE level was used instead of an SPT size cutoff, because the latter is poorly predictive of a positive reaction on food challenge.7 The same criteria for egg allergy were used for peanut allergy, except the SPT peanut and serum-specific IgE cutoff levels used were ≥8 mm and >14 kUA/L, respectively. Children who had propofol more than once had to fulfill the criteria for egg/soy allergy in order for each administration to be included in the analysis.

Children were excluded if they were tolerating whole egg (i.e., boiled or scrambled egg) or soy, or if the SPT/serum-specific IgE levels were not performed within 12 months of propofol administration. SPT cutoff levels to egg white of ≥7 mm, peanut of ≥8 mm, and specific IgE levels for egg (>7 kUA/L), peanut (>14 kUA/L), and soy (>30 kUA/L)8 were deemed to be >90% predictive in diagnosing IgE-mediated egg, peanut, and soy allergy, respectively, based on published data.6,11 It is standard practice to use the SPT to egg white, considered to be the more allergenic part of the egg, to both confirm sensitization and predict the chance of an immediate reaction to whole egg.11

The Australasian Society of Clinical Immunology and Allergy’s definition of an immediate clinical allergic reaction (anaphylaxis or nonanaphylaxis) was used.5 SPTs were performed using a standard lancet technique as previously described.12 All skin test allergens were performed using commercial extracts (peanut and egg allergens from Alyostal, supplied by Link Medical Products Pty Ltd, Sydney, Australia; and histamine 10 mg/mL and negative control solution from Hollister-Stier, supplied by Link Medical Products). These commercial extracts of egg white and egg yolk are manufactured from whole egg white and egg yolk, respectively, and contain the range of allergenic protein(s) to which egg allergy patients can react. Serum-specific IgE levels were performed using the UniCAP system (Pharmacia, UniCAP system, FEIA Phadia, Uppsala, Sweden).

Two main propofol preparations were in use at CHW during the 11-year period, which included Fresofol (supplied by Fresenius Kabi Australia Pty Ltd, Sydney, Australia) (used between 1999–2002 and 2006–2008), and Propofol Sandoz (supplied by Sandoz Pty Ltd, Sydney, Australia) (used from 2003–2005 and 2009 onward). Diprivan (supplied by AstraZeneca, Sydney, Australia) was also available for use during the entire study period. Fospropofol was never used. According to the Australian manufacturer’s product information, Fresofol and Diprivan contain sodium hydroxide (E524), and Diprivan also contains EDTA (EDTA; E385). Propofol Sandoz has no preservatives listed.

Data were analyzed using MINITAB for Windows (Minitab Inc., State College, PA). Continuous data were described as either the mean (±SD) or median (range) if not normally distributed.

### RESULTS

A total of 1162 egg-allergic patients were identified by the search. Of these, 230 had undergone a procedure under anesthetic, with only 42 patients (71 episodes) having propofol administered. Fourteen patients were subsequently excluded because of documentation of eating whole egg without reaction before propofol administration (n = 10), SPT to egg white was 0 mm (n = 2), >12 months had lapsed since last SPT to egg (n = 1), or incomplete documentation (n = 1). None of the excluded children had an allergic reaction to propofol. No child with soy allergy who had received propofol was identified. Twenty-eight egg-allergic children with 43 episodes of propofol administration remained for analysis.

Twenty-one children (75%) were male, and the median age at the time of anesthesia was 2.4 years (range, 1–15 years). The majority of children were younger than 5 years at the time of their first propofol administration (<5 years, n = 21, 75%; 5–10 years, n = 5, 18%; >10 years, n = 2, 7%). Children frequently had documented atopic disease at the time of their first propofol administration, including eczema (n = 17 of 28, 61%), asthma (n = 9 of 28, 32%), or peanut allergy (n = 12, 43%). Three children (11%) had a history of documented drug allergy (rash due to penicillin [n = 1] and amoxicillin/clavulanic acid [n = 1]) and allergy not specified to erythromycin [n = 1]).

Nineteen children (68%) had a history of a clinical allergic reaction to egg, with most having had a reaction in the preceding 24 months, and in most cases the reaction was mild or moderate in severity (Table 1). Only 2 patients

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**Table 1. Last Documented Reaction to Egg Before First Propofol Administration (n = 19)**

<table>
<thead>
<tr>
<th>Time period since last reaction to egg and first propofol administration</th>
<th>Anaphylaxis</th>
<th>Nonanaphylaxis</th>
<th>Eczema flare</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 mo</td>
<td>7 (37%)</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>12–24 mo</td>
<td>8 (42%)</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>&gt;24 mo</td>
<td>4 (21%)</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

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had a history of egg anaphylaxis. The remaining 9 children had never ingested egg because of strongly positive SPT reactions (≥7 mm) to egg white. All patients had a positive SPT (≥3 mm) to egg yolk (median, 6 mm; range, 3–10 mm), and as per standard practice at the CHW, were asked to avoid whole egg white and egg yolk.

One patient with egg anaphylaxis had a soy-specific IgE level of 33 kUA/L 3 months before propofol administration, but was drinking soy milk on a daily basis without any history of an immediate reaction.

Twelve of the egg-allergic children also had a peanut allergy. Five of these had a history of an IgE nonanaphylactic reaction, and the remaining 7 had never ingested peanut and avoided it on the basis of a strong peanut SPT reaction (≥8 mm). Thirteen children (46%) had been prescribed an adrenaline auto-injector because of their food allergy.

Most children (n = 19 of 28, 68%) had a single episode of propofol administration, whereas some had propofol on 2 (n = 5), 3 (n = 2), or 4 (n = 2) separate occasions. Endoscopy was the most common procedure performed (n = 33 of 43). The mean dose of propofol injected was 1.6 mg/kg (SD 0.9). Propofol was the sole drug used in 3 cases (7%), and in another 29 cases (67%), a volatile anesthetic was the only additional drug administered.

There was only 1 allergic reaction after propofol administration. This was in a 7-year-old boy with a history of multiple IgE-mediated food allergies to egg, cow’s milk, nuts, and sesame, who had never had a general anesthetic, propofol, or intralipid. At 4 years of age, he had an exquisite sensitivity to egg, having had an anaphylactic reaction (i.e., pallor, floppy, and urticaria) after sucking on a piece of confectionary containing egg albumin. Consequently, he avoided all egg, including products containing baked egg (e.g., biscuits and cakes). He had a nonanaphylactic reaction (urticaria) to cow’s milk formula at 2 months of age, and had never ingested nuts or sesame because of positive SPT or specific IgE levels to these foods. Before his propofol infusion, he was drinking soy milk without a problem, despite a positive SPT and serum-specific level to soy of 3 mm and 33 kUA/L, respectively (both done 3 months before propofol administration). His SPTs were also positive to egg (7 mm) and peanut (6 mm).

His egg allergy was noted on his anesthetic chart. He received 2 doses of Fresofol and had sevoflurane during an endoscopy for investigation of eosinophilic esophagitis. He had 50 mg propofol at 10:30 AM and then a second dose of 20 mg close to 11:00 AM; the reason for the second dose was unclear from the anesthetic notes. Fifteen minutes after the last dose of propofol (at 11:15 AM), while in the recovery room, he developed generalized erythematous rash an hour later. It is likely that the vast majority of egg-allergic individuals are able to tolerate egg lecithin. This is likely because egg lecithin is derived from less allergenic egg yolk (compared with egg white), and approximately 75% of egg-allergic children are able to tolerate egg yolk without reaction. Furthermore, the amount of any residual egg yolk protein in egg lecithin is likely to be insufficient to be able to induce an allergic reaction in almost all egg-allergic patients.

The amount of contaminant egg or soy protein in propofol has not been examined. Lizaso Bacaicoa et al. demonstrated negative SPT and intradermal testing to egg and soy lecithin and propofol in 20 patients with egg allergy. None of these patients, however, went on to having propofol administered. They also reported intralipid 10% and 20% had a protein contaminant content of 0.75% and 1.4%, respectively. This is relevant because 10% intralipid has the same egg lecithin/soy oil content as some propofol preparations, whereas 20% intralipid has double the amount of soy oil. The authors, however, did not determine
the specific type of the contaminant protein. Martin-Hernandez et al. specifically quantified the amount of egg protein in egg lecithin and found that all of the egg protein was derived from egg yolk, with a very low protein contamination level of 0.005% (or 50 ppm).

In our study, the highest dose of propofol given to a child was 80 mg, equivalent to 8 mL propofol based on a vial of 10 mg/mL. Propofol Sandoz contains 12 mg/mL egg lecithin; hence, the amount of residual egg protein, assuming a contamination level of 0.005%, is estimated to be 5 μg. This amount would be regarded as insufficient to induce an allergic reaction on oral challenge in egg-allergic patients, with 200 μg egg protein being the lowest observed threshold to induce an allergic reaction in an egg-allergic patient.

However, the risk of an allergic reaction is considered to be higher if the allergen is administered by the parenteral route. Recent studies on the safety of egg containing H1N1 vaccines have shown it to be safe in the majority of egg-allergic children. In one of the largest prospective studies performed, 2% of nonanaphylactic egg-allergic children (n = 17 of 830) had an allergic reaction after H1N1 vaccination, in which the vaccine contained as little as 0.03 μg ovalbumin (an egg white protein). However, this rate was not statistically significantly different to the allergic reaction rate reported in the non–egg-allergic control group (3%). Furthermore, few egg-allergic children who had been tolerating baked egg had a mild allergic reaction to the H1N1 vaccine (n = 4 of 251, 1.6%; Gaston De Serres, personal communication, Quebec, Montreal, 2011). Some have therefore recommended that any child with an egg allergy tolerating baked egg or at least a teaspoon of cooked egg (equivalent to 0.6 g egg protein) are at low risk of reaction, and could have the H1N1 as a single dose. It may therefore be reasonable to assume that children with egg allergy tolerating similar amounts of egg protein would also be at very low risk of having an allergic reaction to propofol. It was not possible to determine from the notes in this study the number of children tolerating baked egg.

We had identified no child with soy allergy. Soybean oil was initially thought to be unable to induce allergic reactions and to be safe in soy-allergic individuals. However, there have been rare reports of soy-allergic individuals reacting to soy oil. Soy allergenic proteins have also been found in soy oil, but at concentrations (1.4 ppm) much lower compared with those found in soy lecithin (232–1388 ppm) and to egg yolk protein detected in egg lecithin (50 ppm). Although the negligible protein content soy oil would suggest that most children with soy allergy would tolerate propofol, more data are required before advocating its use in this group of individuals.

Peanut allergy is listed as a contraindication in the product information of Fresofol, possibly because of potential uncommon clinical cross-reactions between peanut and soy. In our series, none of the 12 peanut-allergic individuals without soy allergy had a reaction to propofol. We would recommend any child with a history of peanut allergy without soy or severe egg allergy could have propofol administered.

One child in our series had a nonanaphylactic reaction after his first propofol administration. The child had a history of egg anaphylaxis allergy after consuming very small amounts of egg protein. Although he had a positive reaction to propofol on his SPT, we were unable to determine whether the child was sensitized to the residual egg allergens or the isopropyl/phenol groups on propofol. One other child in our series with egg anaphylaxis with a strongly positive SPT to both egg (11 mm) and peanut (9 mm) had no reaction after their first and only exposure to propofol. We therefore recommend any child with an egg allergy who has a suspected reaction to propofol have an SPT and intradermal testing to the propofol solution and 10% Intralipid as described by Laxenaire et al. A guide to interpretation of the results for such testing is suggested (Table 2).

Our study was limited by our sample size, consistent with current Australian manufacturers’ warning regarding the use of propofol in egg-allergic individuals. Furthermore, we did not examine the rate of propofol hypersensitivity in a control group of non–egg-allergic children. However, one author, DB, noted that there had been no other children with propofol allergy presented at regular anesthetic meetings over the preceding 11 years. Our study also only focused on a pediatric population; however, this is appropriate because the majority of IgE-mediated egg/soy allergy occurs in this population. It is likely that these results would be applicable to adults with persisting IgE-mediated egg/soy allergy.

Propofol is likely to be safe in most egg-allergic children. However, there were only 2 patients with a history of egg anaphylaxis in this study; therefore, until further evidence from a prospective study is available, we suggest that propofol should not be administered to any child with a history of egg anaphylaxis.

### Table 2. Interpretation of Allergy Testing in Egg-Allergic Patients with Hypersensitivity Reactions to Propofol

<table>
<thead>
<tr>
<th>Propofol solution skin prick and/or intradermal result</th>
<th>10% Intralipid solution skin prick and/or intradermal result</th>
<th>Interpretation and recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Allergy likely to isopropyl or phenol groups on propofol</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Allergy may be due to contaminant egg yolk protein. Discuss with an allergist option of an oral challenge with egg lecithin or egg yolk in hospital</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Allergy may be due to isopropyl or phenol groups receiving propofol and/or egg/soy contaminant protein. Suggest alternate for future anesthesia (e.g., inhaled or fospropofol)</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Consider reaction to other administered drugs, other potential allergen source (e.g., latex), or anaphylactoid (non-IgE) reaction to propofol</td>
</tr>
</tbody>
</table>

Ig = immunoglobulin.
REFERENCES


