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Propofol and food allergy

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'How do you like your eggs in the morning?' begins the song made famous by Dean Martin and Helen O'Connell in 1975. If you are one of the 1 in 1000 of the population who is allergic to eggs,[1] the answer to the question posed in the song might be 'No eggs for me, thank you'.

Shortly after the song became a hit, Brian Kay, a UK anaesthetist, conducted the first clinical trial of propofol in Professor Rolly's department in the Belgian city of Ghent, surely one of the most important trials in the history of anaesthesia.[2] A significant clinical question hanging in the air since the subsequent clinical launch of propofol is whether anaesthetists should avoid propofol in patients with specific food allergies. It is remarkable that almost 40 years have elapsed between the first clinical trial of propofol and the fog finally clearing around the putative association between food allergy and hypersensitivity to propofol.

The formulation of di-isopropylphenol used in the initial clinical trials contained Cremophore EL and ethyl alcohol as solubilizing agents. Pain on injection was very common; consequently ethyl alcohol was removed and the concentration of di-isopropylphenol was reduced from 2 to 1%. Cremophore was implicated in triggering severe anaphylactic reactions to the i.v. anaesthetic Althesin (alphaxolone and alphadolone), which was withdrawn from human use in the mid 1980s. A number of hypersensitivity reactions occurred during the early clinical trials of propofol. Consequently, Chremophore and ethyl alcohol were replaced by a lipid emulsion before the preparation was eventually introduced to the market. Several different formulations of propofol are currently available, with different constituents. A commonly-used formulation contains a soybean oil emulsion with long-chain triglycerides, glycerol, egg lecithin (phospholipids), and disodium edetate (EDTA) as an antimicrobial agent. The proportion of long-chain and medium-chain triglycerides may differ between formulations available from different manufacturers. Some preparations may contain sodium metabisulfite or sodium benzoate as a preservative, rather than EDTA. Fospropofol is a recently-introduced water-soluble pro-drug of propofol and is preservative-free.

Propofol was developed in a regulatory environment where there was heightened concern about potential allergic reactions to anaesthetic drugs, and attention became focused on any constituent that might conceivably trigger an allergic reaction, such as lecithin, derived from egg yolk. The pharmaceutical processing of egg lecithin removes or significantly modifies the proteins that could theoretically cause allergy, but concerns persisted. In addition, allergy to egg is almost invariably the result of sensitization to ovalbumin or ovomucoid proteins found in egg-white but not in yolk.

So, how did the putative association between food-allergy and propofol-allergy arise? It is interesting to examine the evidence. In 1994, Bassett and colleagues[3] reported the development of widespread pruritus after the administration of propofol in a single patient who happened to be allergic to egg and suggested that a history of egg-allergy may have to be considered before the administration of propofol. In 2001 Nishiyama[4] reported bronchospasm in two patients after receiving propofol, associated with cutaneous flushing in one of the individuals. No testing for propofol or other allergy was performed. The authors surmised

that soybean oil and yolk lecithin might have induced an allergic reaction, despite the only allergy reported by these patients being allergic rhinitis (hayfever). Hofer and colleagues[5] described hypotension and exacerbation of bronchospasm in a severely-asthmatic child after the administration of propofol and rocuronium. The patient was known to be allergic to egg and peanut, but not soy. No allergy testing was performed to exclude (the more likely) anaphylaxis to rocuronium, and the clinical features were attributed to propofol allergy. The authors concluded that propofol has the potential to cause life-threatening hypersensitivity reactions in patients with allergies to egg and/or soybeans. Thus, with somewhat speculative evidence, allergy to egg, peanut and soy had been causally-associated with propofol allergy. The connection with peanut allergy arose because approximately one third of peanut-allergic individuals are also allergic to soy.[6]

Hypersensitivity to EDTA has been described recently, causing urticaria, flushing and pruritus.[7] This phenomenon appears to be IgE-mediated and skin-testing with EDTA might be considered in patients who have been diagnosed with allergy to an EDTA-containing formulation of propofol, to establish whether the induction agent or the preservative is the cause. EDTA is also found in some radiocontrast media.

Hypersensitivity to sodium metabisulfite is well-described, and the same diagnostic considerations apply in patients who are allergic to preparations of propofol containing this preservative.

Anaphylactic reactions to propofol are infrequent. In a review of perioperative anaphylaxis, Hepner[8] reported an incidence of 1:60 000, but this would seem to be a considerable over-estimate, equating to 40 patients per annum in the UK, if propofol usage data from Royal College of Anaesthetists NAP5 activity survey is taken into consideration.[9] Approximately 2.4 m patients receive propofol each year in the UK. Laxenaire[10] reported 14 patients occurring in France over a five yr period. In the same country, Mertes[11] reported 24 patients over an eight yr period up to 2004. An earlier denominator survey estimated that the total number of anaesthetic procedures in France was approximately double that reported in the UK.[12] Perioperative anaphylaxis is the subject of NAP6, which will start to collect prospective UK-wide data in November 2015.

Accepting that the evidence supporting an association between particular food-allergies and propofol-allergy is tenuous, is there any evidence to the contrary? This information could be obtained in three ways: first, by administering a propofol challenge to patients known to be allergic to these foods; second, by investigating whether patients with food-allergy exhibit a higher incidence of perioperative hypersensitivity to propofol than those without food-allergy; and third, by establishing whether allergy to these foods is significantly more frequent in patients known to have experienced anaphylaxis to propofol than in the general population. Because food-allergy is vastly more common than propofol-allergy, the third option would not yield reliable results.

Identification of the trigger-agent in patients with perioperative anaphylaxis is a specialized undertaking. The exact circumstances and chronology of the event are of overriding importance. The sensitivity and specificity of allergy tests vary between different allergens. For example, skin tests for allergy to neuromuscular blocking drugs are relatively accurate, but the sensitivity of skin testing for the penicillins is only around 70%, (i.e. almost one third of patients are missed when skin testing alone is relied upon). Some drugs are liable to produce false-positive skin tests unless the dilution is carefully controlled. In the case of other drugs, the sensitivity and specificity of allergy tests is simply unknown. Very few CE-marked specific IgE tests are available for the agents encountered during anaesthesia, and they often lack adequate sensitivity.

Identifying propofol as the trigger agent in perioperative anaphylaxis is not straightforward, because propofol hypersensitivity is so infrequent that the predictive power of individual tests and combinations of tests has not been characterized to the same extent as many other drugs. It has been suggested that intradermal testing is more reliable in diagnosing propofol allergy than skinprick.[10]

There is an unequal reciprocal relationship between sensitization and allergy. Patients who are allergic have been sensitized to a particular part of the chemical structure, but not all sensitized patients demonstrate clinical allergy. The majority of tests for 'allergy' actually test for sensitization; skin tests and specific-IgE blood tests fall into this category. Futhermore, the clinical features commonly associated with drug allergy can occur as a result of non-allergic hypersensitivity, in which case, tests for allergy are negative. Thus, a patient who has experienced even severe non-allergic anaphylaxis to atracurium (non-specific histamine release), or a non-steroidal anti-inflammatory drug (cox-inhibition pathway), will have negative skin tests at the appropriate diagnostic dilution. Challenge tests possess the advantage of revealing both allergic and non-allergic hypersensitivity. Graded challenge testing is not possible for neuromuscular blocking drugs but this intervention is commonly performed with antibiotics and some other drugs, and is central to the diagnosis of food allergy. Challenge testing is generally safe, but patients with severe challenge-induced anaphylaxis have been reported and appropriate precautions must be taken.[13]

In this issue of the British Journal of Anaesthesia, Asserhøj and her colleagues in Denmark[14] report an investigation in which they set out to establish the frequency of anaphylaxis to propofol over an eight year period (Part A) and to investigate whether patients sensitized to egg, soy or peanut tolerated propofol (Part B). This is an important study because it stimulates discussion surrounding the diagnostic pathway for suspected propofol-hypersensitivity, and finally lays to rest the putative connection between propofol hypersensitivity and allergy to egg, soy and peanut.

153 patients underwent a panel of tests for allergy to all the substances they encountered within a specified time before the onset of perioperative anaphylaxis. One or more tests for propofol hypersensitivity was positive in four patients. The testing protocol was unusual in including challenge testing with propofol in addition to skinprick and intradermal tests. Their protocol dictated that patients underwent challenge testing even if the skin tests were positive. The combination of skinprick and intradermal tests is very sensitive[10] and would have established with a high level of certainty that the patients were allergic to propofol. The authors could be open to criticism for proceeding to challenge testing with propofol when it was already known that the patient was allergic to that drug, with the potential consequence of eliciting a severe iatrogenic anaphylactic reaction. Nonetheless, challenge testing increased the number of patients diagnosed with hypersensitivity to propofol from one to four. The patient known to be allergic to propofol had previously exhibited positive skinprick and intradermal tests, together with an increase in mast cell tryptase, indicating an IgE-mediated mechanism Thankfully, challenge testing did not provoke an anaphylactic reaction. Since 2014, this group of investigators has not proceeded to challenging with propofol if one or more skin tests are positive. Unfortunately the investigators were not able to investigate whether the reactions were the result of hypersensitivity to propofol or one of the other constituents of the commercial preparations and further work is needed to elucidate this aspect. The authors raise the interesting

prospect that non IgE-mediated hypersensitivity to propofol might be more frequent than IgE-mediated allergy to this drug. It follows that individuals in whom propofol-hypersensitivity is suspected should be offered i.v. challenge testing with propofol if (a) all other possible triggers have been excluded, and (b) skinprick and intradermal tests with propofol are negative. The authors calculated that the incidence of propofol-hypersensitivity in Denmark is approximately 2.2 per million. This is likely to be a reasonably accurate estimate as there is a single Danish centre for the investigation of perioperative anaphylaxis, although the number of propofol anaesthetics administered in Denmark is not accurately known.

Part B of the Danish study investigated whether patients who tested positive for specific-IgE to peanut and/or soy and/or egg at a specialist food allergy clinic developed clinical features of hypersensitivity when they were exposed to propofol during anaesthesia and surgery. This was a retrospective study: patients were identified at the food allergy clinic, and their anaesthetic records were examined for evidence of a hypersensitivity reaction. In addition, a questionnaire soliciting a history of allergic symptoms to these foods was sent to patients. 544 patients were identified and the anaesthetic records of 99 patients who received propofol anaesthesia were examined. Some patients received multiple propofol anaesthetics; the total number of exposures was 171. All 99 patients were sensitized to peanut and/or soy and/or egg but clinical allergy was reported in only 44. No patient developed clinical features suggestive of hypersensitivity during anaesthesia.

The Danish study corroborates the recent study from Spain[15] in which 52 adult patients sensitized to peanut and/or soy and/or egg underwent propofol sedation for repeated endoscopic procedures without observing any events suggestive of hypersensitivity.

Although there can be little doubt that there is no contraindication to administering propofol to adults who are allergic to peanut and/or soy and/or egg, it would be appropriate to sound a note of caution in children. An Australian study[16] reviewed 43 propofol administrations in 28 children known to be allergic to egg. A seven yr old child experienced generalized urticaria and erythema 45 min after the first dose of propofol, 15 min after a second dose. The patient had experienced anaphylaxis to egg aged four. The timing of the appearance of the clinical features suggests either a non-IgE mediated reaction to propofol, or that a different trigger was responsible. A skinprick test was just positive at 3 mm, but intradermal testing was not performed and the possibility that this was a false-positive result cannot be discounted. Although there is convincing evidence that propofol is safe in children with mild or moderate egg-allergy, it may be prudent to avoid propofol in children who have experienced anaphylaxis to egg, until more evidence is available. There is no persuasive evidence that propofol administration is unsafe in children who are allergic to peanut or soy.

So where does this leave us? The situation in adults is straightforward: there is convincing evidence that propofol is safe in patients who are allergic to peanut and/or soy and/or egg. Further research is required before children who have experienced severe anaphylaxis to egg can be given propofol with confidence of safety.

Declaration of interest

None declared.

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Clinical Practice

No evidence for contraindications to the use of propofol in adults allergic to egg, soy or peanut†

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Abstract

Background: Propofol is thought to be a potential cause of allergic reactions in patients allergic to egg, soy or peanut, since current formulations contain an emulsion that includes egg lecithin and soybean oil. However, other than six case reports lacking in confirmatory evidence of an allergic reaction, there is no evidence linking the two types of allergies. The aim of this study was to examine the frequency of propofol allergy and to investigate if patients with specific immunoglobulin E (IgE) to egg, soy or peanut tolerated propofol.

Methods: Study A examined the frequency of propofol allergy in 273 patients systematically investigated for suspected perioperative allergic reactions. Of these, 153 had been exposed to propofol and underwent skin tests and intravenous provocation. Study B retrospectively investigated propofol exposure and tolerance in 520 adult patients with a positive specific IgE to egg, soy or peanut.

Results: Four of the 153 propofol-exposed patients (2.6%) investigated in study A were diagnosed with propofol allergy. Of these, three tested positive only on intravenous provocation. None of the four had allergic symptoms when eating egg, soy or peanut and none had detectable levels of specific IgE to egg or soy in their serum. In study B we found no signs of allergic reactions towards propofol in 171 retrieved anaesthetic charts from 99 patients with specific IgE to egg, soy or peanut.

Conclusion: No connection between allergy to propofol and allergy to egg, soy or peanut was found. The present practice of choosing alternatives to propofol in patients with this kind of food allergy is not evidence based and should be reconsidered.

Key words: anaphylaxis; egg hypersensitivity; i.v. anaesthetics, propofol; peanut hypersensitivity; soybean oil

Editor's key points

- The evidence for a link between allergy to certain foodstuffs and to propofol is weak.
- The authors studied a cohort of adults being investigated for a suspected perioperative allergic reaction.
- Separately they analysed anaesthetic charts of other patients recently diagnosed with food allergies.
- They found no evidence of a link between propofol allergy and allergy to soy, peanut or egg.

Propofol is frequently used for induction and maintenance of general anaesthesia and is also a commonly used sedative for short procedures and in intensive care units.[1] It is marketed as an emulsion containing soybean oil, egg lecithin and glycerol.[1] Initially no contraindications were stated in product leaflets, but in recent years contraindications against its use in individuals allergic to soy, peanut and egg lecithin have emerged in many countries.[2]

Allergic reactions to propofol are rare, with a previously estimated incidence of 1:60.000 exposures.[3] Several cases of allergic reactions to propofol have been published,[4–10] with no mention of

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egg, soy or peanut allergy. There are six published case reports of suspected allergy to propofol in individuals allergic to egg, soy or peanut.[11–15] However, these are lacking confirmatory evidence, as skin tests or intravenous provocations with propofol were either not performed or found negative, except in one case.[15]

Although British and French guidelines state that there is no evidence that propofol should be avoided in patients allergic to egg or soy, they still suggest caution.[16 17] Conflicting statements and lack of evidence lead to confusion among clinicians, thus the aims of this study were to examine the frequency of confirmed propofol allergy and concomitant allergy to egg, soy or peanut and to investigate if patients with suspected food allergy and specific immunoglobulin E (IgE) to egg, soy or peanut had subsequently tolerated propofol.

Methods

There was no overlap between the cohorts in study A and B.

Study A

A retrospective study of 273 patients investigated in the Danish Anaesthesia Allergy Centre (DAAC) during 2004–11 due to a suspected perioperative allergic reaction. Of these, 153 (56%) had been exposed to propofol. All patients investigated in the DAAC have their charts reviewed and are then subjected to a standardised investigation program testing all drugs and substances they have been exposed to if one of the following criteria apply to the suspected reaction: intravenous exposure <1 h before onset of reaction or other exposures (oral, subcutaneous, local, epidural, spinal etc.) <2 h before onset of reaction. If there is a positive reaction to a drug or substance, then investigations for other drugs/substances are continued, as a small number of patients react to more than one agent.

The investigation programme included the following tests:

- Serum tryptase (Thermo Fisher Scientific, Uppsala, Sweden). Tryptase is released from mast cells during an IgE-mediated allergic reaction and is used to help confirm an allergic mechanism. Values at the time of reaction should always be compared with the patient's own baseline value.[18]
- Specific IgE (ImmunoCAP method, Thermo Fisher Scientific, Uppsala, Sweden). This test measures IgE antibodies in the blood directed at a specific allergen. Values >0.35 kUA litre^{-1} are considered positive.
- Skin prick test (SPT). This is a skin test carried out in duplicate on the forearm. Negative control tests are made with saline and positive control tests with histamine. Development of a wheal ≥3 mm in diameter after 20 min is considered positive.
- Intradermal test (IDT). This is a skin test carried out in duplicate on the back. Negative control test is made with saline. The test is considered positive when a wheal develops with a mean diameter ≥ twice the diameter of the negative control after 20 min.
- Intravenous provocation tests. Provocation tests are performed for all substances to which the patient was exposed (except for neuromuscular blocking agents, chlorhexidine and latex). The agent most likely to have been responsible for the reaction is tested last. Propofol provocation tests comprise a three-step titrated i.v. provocation up to a maximum dose of 10 mg propofol. A provocation test is considered positive when symptoms from the initial reaction are reproduced.

The maximum skin test concentrations of propofol used in SPT and IDT were recommended by the French anaesthesia allergy guidelines from 2002[19] and are still used today.[20] Investigations are carried out in a highly specialised setting with resuscitation facilities and anaesthetic personnel available and continuous monitoring of patients during provocations. All patients have intravenous access. For the first years in the DAAC, all investigation modalities were carried out for all drugs to gather information on the sensitivity and specificity of the individual tests. Since 2014, a drug is defined as being responsible for an allergic reaction if at least two of the following tests are positive: SPT, IDT, specific IgE or drug provocation tests.[21 22] If two of the first three tests are positive, then drug provocation tests are no longer performed.

Study B

A retrospective study was conducted including all patients ≥16 yr of age tested for specific IgE to egg, soy or peanut as part of investigations for suspected food allergy in the Allergy Clinic at Gentofte Hospital during 2004–12. Approval was obtained from the local research ethics committee to contact patients and send them a questionnaire. Data storage was approved by the national Data Protection Agency.

A total of 1290 patients were included in study B (see Fig. 1). Of these, 544 patients had positive specific IgE for egg and/or soy and/or peanut. Specific IgE values >0.35 kUA litre^{-1} were considered positive and defined as a sign of allergic sensitisation. Onset of sensitisation was therefore defined as the time of positive specific IgE analysis. A total of 24 patients were excluded due to death, emigration or mismatch between patient identification and blood sample. Thus a questionnaire was sent to 520 patients. The questionnaire included questions on allergic symptoms when eating egg, soy or peanut; history of previous surgery and anaesthesia; and a request for consent to collect anaesthetic charts and recovery notes from previous surgeries and anaesthesia. If patients did not reply, an attempt was made to contact them by phone and subsequently one reminder was sent ~2 months after the initial letter.

When a positive reply was received, the patient's records were identified based on information from the questionnaire; in addition, the National Patient Identification System was searched. Anaesthetic charts and recovery notes were retrieved for surgeries taking place both before and after the onset of sensitisation.

Anaesthetic charts and recovery notes from previous surgeries were reviewed to look for any indication of an allergic reaction. An allergic reaction was considered possible if one of the following criteria was met: a written comment about a specific allergic symptom (e.g. skin rash or pruritus) or a mention of suspicion of an allergic reaction on the anaesthetic chart or postoperative notes or administration of antihistamines, corticosteroids or epinephrine during surgery or in the postoperative period. Pretreatment with antihistamines was also noted, as this might potentially mask a minor allergic reaction.

Results

Study A

The 153 patients exposed to propofol before the suspected perioperative allergic reaction underwent standardised investigations for all drugs and substances they had been exposed to, including propofol. SPT was performed in 152 (99%) patients (one missing data) and 149 of 153 (97%) had IDT performed with propofol. Intravenous provocation was performed in 133 of 153 patients (87%).

Of the 153 patients exposed to propofol, only 4 (2.6%) tested positive for propofol on one or more of the tests performed. All

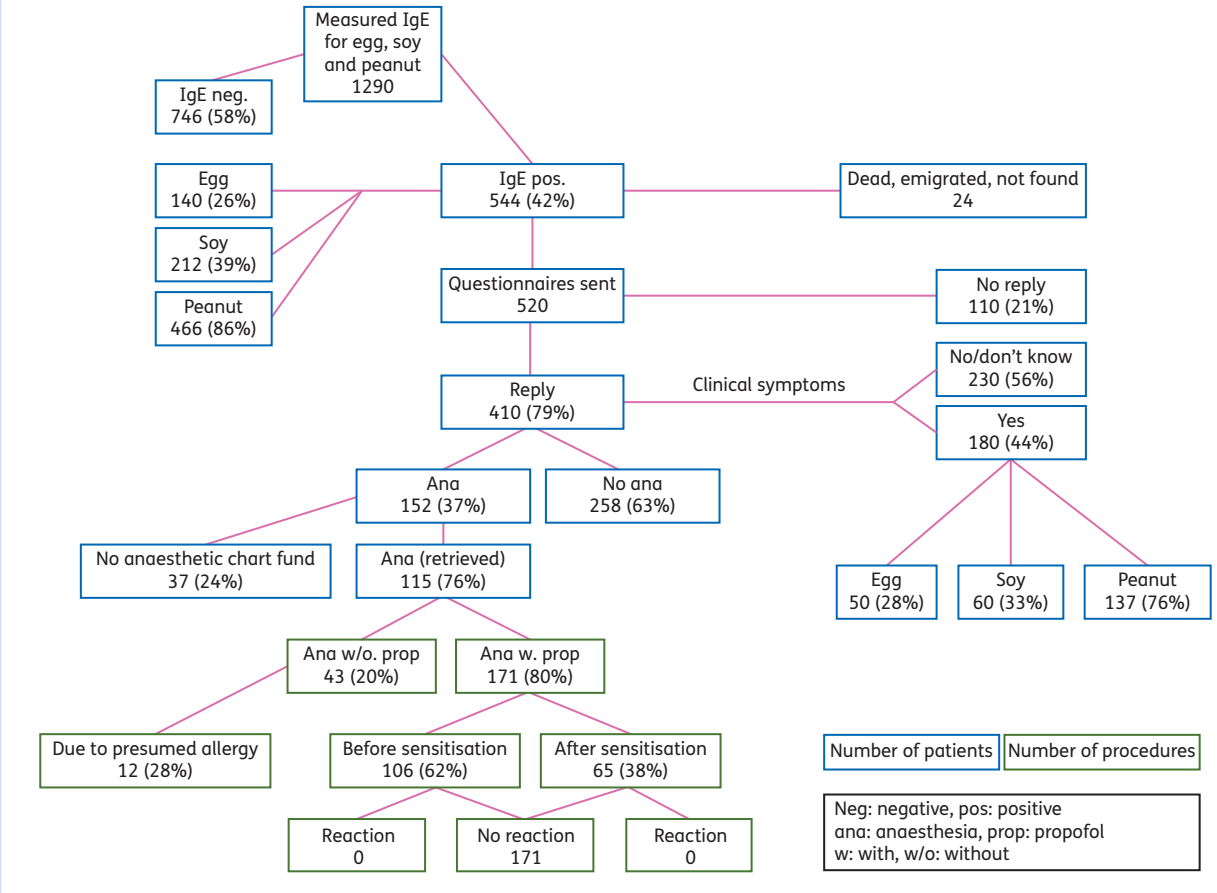

Fig 1 Flowchart study B.

four tested negative to other drugs and substances they had been exposed to prior to the perioperative reaction. See Table 1 for clinical details and investigation results for these four patients. All four had positive intravenous provocation leading to reproduction of hypersensitivity symptoms experienced during the original reaction, mainly pruritus, flushing and swelling. Only one patient had positive skin tests and an elevated serum tryptase, which might indicate an IgE-mediated allergy to propofol. When questioned, none of the four patients reported clinical reactions to egg, soy or peanut and all had negative specific IgE for egg or soy.

Study B

The results of study B are shown in the flowchart in Fig. 1. Of 1290 patients tested for specific IgE to egg, soy or peanut, 544 (42%) had one or more positive tests [egg 140 patients (26%), soy 212 patients (39%), peanut 466 patients (86%)]. In total, 24 patients died, emigrated or were not found. A total of 410 of 520 patients (79%) with IgE to egg and/or soy and/or peanut responded to the questionnaire. The gender and age distribution for the 410 responders was 154 males (38%) with a mean age of 39 yr (range 16–78) and 256 females (62%) with a mean age of 40 yr (range 16–81). In the group of 110 non-responders, 48 were male (44%; mean age 34 yr) and 62 were female (56%; mean age 34 yr). Of the 410 responders, 180 (44%) had clinical allergy, i.e. reported allergic symptoms when eating one or more of egg (28%), soy (33%) or peanut (76%). The remaining 230 patients (56%) did not recall having any allergic symptoms to egg, soy or peanut. A total of 152 patients reported having a procedure involving general anaesthesia performed between 1986 and 2012. We were able to retrieve anaesthetic charts from 214 procedures performed on 115 patients (76%). Of the 214 procedures, propofol was used in 171 (80%), exposing in total 99 of 115 patients. Of the 99 exposed patients, 44 (44%) reported having a clinical allergy to egg and/or soy and/or peanut.

Of the 171 procedures using propofol, 65 were performed (in 39 patients) after identified egg, soy or peanut sensitisation. Exposure was repeated (on average 2.8 times) in 13 patients. Of the 39 patients, 5 reported a clinical allergy to egg, 6 to soy and 8 to peanut (of those, 4 reported more than one clinical allergy).

None of the anaesthetic charts or postoperative notes for the 171 procedures using propofol included any remarks indicating possible allergic reactions.

In 17 cases, one of the criteria for a possible allergic reaction was met. None of them were considered relevant and, all together, no indication of an allergic reaction was found:

- In 10 cases, antihistamine pretreatment was given due to other known allergies, thus masking of a potential allergic reaction cannot be ruled out but is considered unlikely.
- In 3 cases, corticosteroid was given during anaesthesia on specific non-allergic indications, such as to reduce postoperative oedema.

Table 1 Clinical details of patients testing positive to propofol in study A. NT, not tested. *Reaction class: 1, mild reactions with generalised cutaneous signs, self-limiting; 2, moderate, multiorgan involvement may be self-limiting; 3, severe, life-threatening, usually multiorgan involvement, requires specific treatment; 4, cardiac arrest.[23] †H, hypotension; T, tachycardia; R, rash; F, flushing; B, bronchospasm. ‡AH, antihistamine; S, steroid; E, ephedrine; F, fluids; P, phenylephrine

Basic data	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Female	Female	Female	Male
Age (yr)	25	20	37	64
Known egg, soy or peanut allergy	No	No	No	No
Information about reaction				
Grade of reaction*	2	1	2	3
Symptoms†	R, H	R	H, F	H, T, B
Treatment‡	E, F	AH, S	AH, S, E, F	E, P, F
Tryptase at time of reaction (μg litre^{-1})	2.11	NT	3.37	82.5
Investigation results				
Baseline tryptase (μg litre^{-1})	3.25	4.61	4.24	4.88
IgE: egg, soy	Negative	Negative	Negative	Negative
Phadiatop (kU litre^{-1})	<0.35	<0.35	<0.35	<0.35
SPT (10 mg ml^{-1})	Negative	Negative	Negative	Positive
IDT (1 mg ml^{-1})	Negative	Negative	Negative	Positive
Provocation (maximum dose 10 mg i.v.)	Positive	Positive	Positive	Positive

- In 3 cases, pruritus was noted in the chart. There were no associated objective symptoms in any of the cases, and pruritus started shortly after injection of an opioid, which has pruritus as a well-known side effect.
- In 1 case, antihistamine was given at the end of anaesthesia. There was no indication of an allergic reaction and it is thought it was given as an antiemetic.

In 43 of the 214 (20%) anaesthetic procedures propofol was not administered. In 12 procedures the anaesthetists had specifically noted that propofol was avoided due to the patient's presumed allergy to egg, soy or peanut. For 10 of the 12 procedures, the patient had reported clinical symptoms of egg and/or soy and/or peanut allergy. The last two procedures were performed in one patient, who had positive specific IgE for soy and peanut but tolerated eating egg, soy and peanut on a daily basis.

Discussion

The discussion about whether propofol should be administered to egg-, soy- and peanut-allergic patients continues in many countries.[11–15 24 25] There are inconsistencies regarding contraindications when comparing product leaflets in different countries. Warnings against the use of propofol in patients allergic to soy, peanut and excipients (egg lecithin, soybean oil, glycerol, sodium hydroxide, water, disodiumetate) are found in Denmark and the UK. In contrast, warnings in the USA only mention patients allergic to egg, soy or excipients, with no warnings against using propofol in patients allergic to peanuts.

In Denmark, over the past few years, increasing concern about the use of propofol in patients with egg, soy or peanut allergy has been reflected in an increase in referrals to the DAAC, with specific mention of suspected allergy to propofol. This increased attention to the subject in the anaesthetic community may be due to the introduction of nurse-administered propofol sedation (NAPS), used for outpatient procedures such as colonoscopies, gastroscopies, bronchoscopies etc., where rigorous checklists including questions on allergies to egg, soy and peanut are followed prior to starting sedation. However, allergic reactions to propofol during NAPS are rare according to a large American study where no allergic reactions were seen in 9152 cases of NAPS, and only 5 patients had not been given propofol, either due to preference or to suspected allergy to components of propofol.[26]

Our study A of patients investigated following suspected allergic reactions during general anaesthesia showed no evidence of a connection with allergy to foods. None of the four patients with confirmed hypersensitivity to propofol in the DAAC had allergy to egg, soy or peanut. A very conservative estimate of propofol use in 50% of the 450 000 anaesthetics used each year in Denmark would suggest a total of 1.8 million exposures to propofol in the 8 yr period investigated. This gives an estimated incidence of propofol hypersensitivity of 2.2 per 1 million anaesthetics in Denmark.

In study B we examined adult patients with specific IgE to egg, soy or peanut and exposure to propofol during general anaesthesia. Despite positive specific IgE, only 44% of the patients had clinical symptoms when eating egg, soy or peanut. No allergic reactions occurred during 171 procedures identified in 99 patients. The ability to tolerate propofol was the same whether or not patients reported clinical symptoms of egg, soy or peanut allergy. Also, there was no difference in tolerance regarding first exposure *vs* re-exposure.

Taken together, our studies of patients undergoing general anaesthesia show no evidence in support of a connection between allergy to propofol and allergy to egg, soy or peanut. Recently, two studies examining patients undergoing sedation with propofol have reached the same conclusion. A Spanish study from 2014 investigated 60 eosinophilic esophagitis (EoE) patients who had 404 upper endoscopies performed under propofol sedation. Fifty-two (86%) of the patients had egg, soy or peanut sensitisation confirmed by either specific IgE or SPT (only 35% reported clinical allergy). There were no allergic reactions and the researchers concluded that propofol can be safely administered to EoE patients regardless of documented sensitisation to egg, soy or peanut.[25]

The other study, from Australia, examined the use of propofol in 28 egg-allergic children undergoing 43 propofol sedations. They found one reaction with generalised erythema and urticaria

in a boy with a history of egg anaphylaxis and multiple other IgE-mediated food allergies. The SPT with propofol was 3 mm and was concluded to be positive. The authors conclude that propofol is likely to be safe in the majority of children allergic to egg.[27]

The conclusion that propofol administration is safe in patients with allergy to egg, soy or peanut is further supported by examining the evidence for the suggested mechanism of propofol allergy. Most cases of allergy to propofol are thought to be IgE mediated[3] and the 2-isopropyl-group of the propofol molecule have been suspected as the reactive epitopes.[4 5 28] In accordance with this, several case reports on anaphylaxis or adverse reactions caused by propofol did not even mention egg, soy or peanut allergy.[6–10]

Three of the four patients in our study had negative skin tests and did not have elevated tryptase at the time of reaction. This suggests a non-IgE-mediated or even non-allergenic mechanism and underlines the need to perform intravenous provocation, as propofol hypersensitivity would have otherwise been missed in these three patients. The fourth patient had elevated tryptase at the time of reaction and positive skin tests to propofol, which is more suggestive of an IgE-mediated mechanism.

Evidence of the allergenic potential of the soy or egg components of propofol is lacking. Soy allergy is rare and tolerance is often achieved in late childhood.[29] Propofol contains refined soybean oil, but the allergenic proteins are removed during the refining process.[30]

Egg allergy is mainly seen in children and is usually outgrown.[31] Egg-allergic patients typically react to proteins from egg whites (ovalbumin, ovomucoid and conalbumin) and not to egg lecithin, from the egg yolk, which is used in propofol.[30–32] Dewachter and colleagues[24] showed that SPT with propofol and egg lecithin were negative in 10 children with clinical egg allergy and SPT with propofol and soybean oil were negative in 3 patients with documented soy allergy.

Regarding suggested cross-reactivity between peanut and soy, a review article from 2000[2] reported a low rate of cross-reactivity. Considering the lack of reported reactions to propofol from the USA, where peanut allergy is common, it is unlikely that the presumed cross-reactivity between soy and peanut has any clinical relevance with respect to propofol allergy.

Interestingly, our study showed that a group of patients were actually deprived of propofol due to sensitisation/allergy to egg, soy or peanut, even though propofol might have been the best choice for the patient. This was mainly the case with patients who reported clinical allergy. However, one patient was deprived of propofol due to positive specific IgE, despite the fact that she tolerated eating egg, soy and peanut. Taken together, there is no real evidence of a mechanistic connection between propofol hypersensitivity and allergy to egg, soy or peanut.

Our studies have some limitations. Study B is a retrospective study and excludes children <16 yr of age, so we cannot draw any conclusions with regard to children and propofol.

It might be argued that our patients may have lost their clinical allergy in the time from IgE testing to propofol exposure. This gap was a maximum of 8 yr, but less than 3 yr for the majority of patients. This, combined with the fact that allergy to egg and soy is mostly outgrown in the teenage years, makes it unlikely to have influenced our study.

Ideally, conclusions on clinical allergy should be based on provocation with egg, soy and peanut rather than patient's recall of clinical allergy. As this was not possible, we instead used positive specific IgE as a sign of allergic sensitisation. However, not all patients with allergic sensitisation (shown by positive specific IgE or SPT) have clinical allergy. For this reason, we chose to report both IgE sensitisation and self-reported clinical allergy.

Different formulations of propofol have been used during the period of investigation. It would have been relevant to examine if hypersensitivity reactions were related to specific formulations of propofol (e.g. LCT *vs* LCT-MCT propofol). Unfortunately, this was not possible since the specific formulation is rarely mentioned in referrals (in study A) or on anaesthetic charts (in study B).

Lastly, the fact that antihistamine was administered preoperatively in 10 of our 171 cases in study B might have masked mild allergic symptoms. However, it is unlikely that pre-administered antihistamine would mask IgE-mediated anaphylaxis.[17]

In conclusion, neither of our studies support a connection between propofol hypersensitivity and allergy to egg, soy or peanut. This, combined with a very weak evidence base in the literature and recent studies showing patients tolerating propofol sedation despite allergy to egg, soy or peanut, suggests that propofol can be administered to these patients in all doses. Therefore the increasing practice of anaesthetists choosing alternatives to propofol in patients with this kind of food allergy is not evidence based and manufacturers of propofol should consider revising their current contraindications to propofol administration in patients allergic to egg, soy or peanut.

Authors' contributions

Data collection and analysis, writing of the first draft: L.L.A.
Initiation of the study, supervision of the study and writing of the manuscript: L.H.G.
Critical comments about study design and the manuscript: H.M., M.K.
All authors approved the final manuscript.

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Declaration of interest

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