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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in triggering severe anaphylactic reactions to the i.v. anaesthetic Althesin (alphaxolone and alphadolone), which was withdrawn from human use in the mid 1980s.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

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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

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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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