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## Severe anaphylaxis to Propofol: first case of evidence of sensitization to soy oil

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### KEY WORDS

*allergenicity; anaphylaxis; propofol;  
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### Summary

*The growing worldwide prevalence of food allergies is drawing attention to the risk of allergenic proteins found in intravenous medicinal products, particularly anaesthetics. Propofol induced anaphylaxis has been described. The presence of soybean oil and egg lecithins in the lipid emulsion highlights their suspected responsibility in certain cases. We report a case of anaphylaxis to propofol in an adult patient without food allergy to soy, but with a latent sensitization to soy. An IgE-dependent allergy to propofol was established by a basophil activation test. Here, we document for the first time the existence of specific IgEs to a 65kDa protein, found in soybean oil and soy flour.*

*In the absence of data on the reactogenic threshold for allergenic food proteins injected intravenously, a risk appears to be established and leads us to recommend a systematic detection for proteins in the refined soybean oil used in the pharmaceutical industry for intravenous products.*

### Introduction

Most intravenous anaesthetics can induce perioperative anaphylaxis. Hypnotics represent 2.34% of cases, and propofol is involved in 55.8% of these cases (1). Because of the rapid onset of anaesthesia, short duration and few adverse effects, these drugs are widely used, not only for anaesthesia but also for sedation during minor outpatient procedures and endoscopic examinations. However, life-threatening reactions such as anaphylactic shock or severe bronchospasm have been reported (2,3).

Propofol is formulated in 10% soybean oil with egg lecithins. We should question the allergenic risk of residual proteins, because the risk of food proteins included in drugs is not negligible (4). Moreover, food allergies represent the second wave of atopic diseases. Up to 10% of pre-school children have food allergies, including egg and soy allergy in Australia and China, with a concordant increase in European countries (5). Cases of anaphylaxis linked to propofol incriminating soybean oil have already been postulated in patients allergic to soy (6-9). The

presence of allergens in soybean oil at risk of triggering an allergic reaction has been established in a single case (10).

We present a case of anaphylaxis linked to propofol in a patient in which, for the first time, sensitization to an allergenic protein found in soybean oil and soy flour was characterised.

### Patient

A patient aged 66 had a general anaesthetic for a gastroscopy. Anaesthetic induction involved an intravenous injection of Diprivan® (propofol). Five minutes later, she had a severe bronchospasm with arterial desaturation, dropping from 100% to 62% in 5 minutes, and her blood pressure fell from 148/90 mmHg to 98/41 mmHg in 10 minutes. There was no tachycardia (pulse between 70 and 90 beats per minute). No skin reactions were noted. The problem was solved after ventilation with high-flow oxygen therapy via a face mask, and an aerosol of salbutamol and ipratropium. Saturation rose to 95% in 10 minutes and blood pressure gradually rose to 117/60 mmHg at 30 minutes, then 120/70 mmHg at 75 minutes.

**Table 1** - Basophil activation test (BAT) to Diprivan® (Propofol).

Tests	% of CD63+, activated basophils	Diprivan®/Negative control ratio (> 2: positive)	+/-
Positive control to anti-IgE	80.98%		
Non-specific positive control to FMLP	41.91%		
Negative control	0.85%		
Diprivan® 100 µg/ml	2.16%	2.54	+
Diprivan® 10 µg/ml	1.95%	2.29	+
Diprivan® 1 µg/ml	1.50%	1.76	-

The endoscopic examination was interrupted.

This patient's prior history was marked by a primary infection with tuberculosis at 4 years old, oesophagitis with bulbar ulcer, pollinosis, hypertension treated with irbesartan, lercanidipine and hydrochlorothiazide, chronic glaucoma treated with timolol eye-drops, and surgery for a uterine fibroma. There was no history of asthma or food allergy.

This patient consulted an allergologist 4 months later. A normal flow-volume curve and body plethysmography confirmed the absence of obstructive or restrictive respiratory disorder. A provocation test with methacholine eliminated bronchial hyperreactivity. On skin normally reactive to 9% codeine phosphate, prick tests

with standard inhalants (Stallergène®, Anthony, France) revealed a monosensitization to birch pollen. The prick test to latex was negative. The prick tests and intradermal reactions were negative for Diprivan® (propofol, 10 mg/ml) and Medialipid® (20% Intralipid) in pure concentrations. Prick tests were positive for soy (5 mm) and soy sauce (4 mm), negative for soybean oil, soy lecithin, raw egg white and yolk, egg lecithin. The basophil activation test performed by flow cytometry (CD63+) was positive to Diprivan® (**table 1**). The specific IgEs (Thermofisher Scientific®, Waltham, USA) were positive for soy seeds (0.4 kU<sub>A</sub>/L), and Gly m 4 (9 kU<sub>A</sub>/L). No specific IgEs for Gly m 5 and Gly m 6 were detected. SDS-PAGE gel electrophoresis was stained with Coomassie

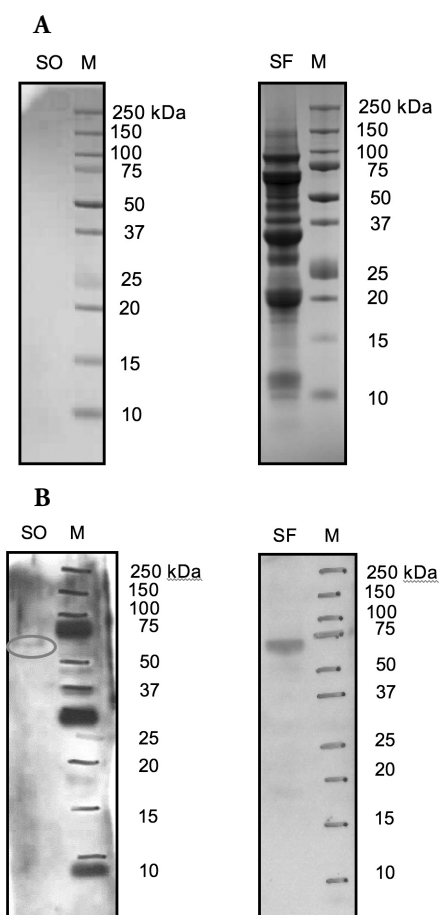
**Table 2** - Propofol induced allergic reactions assigned to food allergy.

Author	Sex	Age (years)	Asthma	Food allergy to Soy, Peanuts, Egg	Symptoms	Skin tests	Specific IgE (kUA/L)	Cell biology
Hofer (2003)	M	1	No	Egg, Peanut oil	Anaphylactic shock	nd	nd	nd
Fontaine (2011)	M	7	Yes	Soy, Peanut	Bronchospasm, urticaria	Positive PT: birch Positive PT: peanut Positive PT: soy	Soy: 1.2 Gly m 4: 4.1	nd
You (2012)	F	74	No	Soy	Bronchospasm SpO <sub>2</sub> 56%, epiglottis angioedema	Positive PT Propofol Positive PT Intralipid	nd	nd
Tashkandi (2010)	M	4	Yes	Milk, Egg, Soy	Atopic dermatitis, anaphylactic shock, bradycardia	nd	nd	nd
Molina-Infante (2014)	M	14	Yes	Nuts	Atopic dermatitis, bronchospasm	Negative PT Propofol Negative PT Intralipid	nd	Negative LHRT: Propofol

PT: prick-test, LHRT: leukocyte histamine release test; nd: not done

Blue (**figure 1A**). The immunoblots for food-grade soy flour and soybean oil with the patient's serum diluted to 1/50th showed a protein of about 65 kDa binding the IgEs (**figure 1B**).

**Figure 1** - A. Electrophoresis stained with Coomassie blue with soy oil extract (SO) and soy flour (SF) separated by SDS-PAGE. B. Immunoblot with soy oil extract (SO) and soy flour (SF): IgE reactive band of a 65 kDa protein.



Legend: M: markers of molecular weight.

## Discussion

Propofol, or 2,6-diisopropylphenol, is a highly lipophilic molecule initially formulated in Cremophor EL. Because of the occurrence of anaphylaxis with the latter, it was thereafter formulated in 10% of soybean oil containing disodium edetate glycol and egg lecithin. The oil droplets (emulsion) have an average diameter of 150 to 300 nm (0.15 to 0.30  $\mu\text{m}$ ), identical in size to chylomicrons (11). Anaphylactic shock with cardiovascular collapse or severe bronchospasm have been described (12-20). Sensitization to the molecule has been implicated because of

known sensitization to the di-isopropyl radical that is found in dermatological topical medications and lipid formulations. It has been confirmed by positive tests to propofol and negative tests to the lipid component (2,12-14,21,22). In a series of 14 cases of anaphylaxis to propofol, 6 had another drug allergy. Intradermal testing was positive to propofol, negative to Intralipid<sup>®</sup>, and the intravenous infusion test with Intralipid<sup>®</sup> was negative (2).

In egg-allergic children, egg lecithins can be incriminated, because cases of food allergy to egg lecithin have been established by oral provocation tests (23). Allergy to Intralipid<sup>®</sup>, a fat emulsion used for parenteral nutrition containing 20% of soybean oil and 1.2% of egg lecithins, was described in an egg-allergic child (24). Of 28 egg-allergic children, corresponding to 43 administrations of propofol, one reaction attributed to egg lecithin was reported. No child with a soy allergy who had propofol was identified (25). Of 52 adults sensitized to egg or soy, with eosinophilic oesophagitis, 404 uses of propofol for endoscopy did not include any accidents. One case of transient bronchospasm occurred with no explanation (17).

The risk of the allergenicity of plant oils has been studied. Non-refined oils and soy lecithins show residual IgE-binding activity (26). Refined oils may even contain tiny amounts of residual proteins (27,28). Available data suggest that the protein content of refined oils is of the order of 1-3  $\mu\text{g/L}$  (29). It has been considered that refined oil is unlikely to contain a significant level of protein allergens (30). However, some cases of anaphylaxis to propofol have been linked to sensitization to soy (6-9,17) (**table 2**).

In a case of anaphylaxis to generic omeprazole containing soybean oil, the presence of IgEs specific to this drug was revealed by dot blot, whereas no IgE binding was observed to the drug without excipient. The dot blot for soybean oil was also positive (10).

The type of residual allergen has not yet been demonstrated. One case of anaphylaxis to propofol in a patient allergic to birch pollen and suffering from cross-sensitization between Bet v 1 and Gly m 4 soy allergen homologous to Bet v 1 led to the suggestion that the responsible allergen could be Gly m 4 (6). In this case of anaphylaxis to propofol, in which IgE-dependent sensitization to Diprivan was established by a basophil activation test, specific IgEs to Gly m 4 (16.7 kDa) were present. However the immunoblot shows the presence of a 65 kDa allergenic protein in soy oil, binding the specific IgEs. The patient was monosensitized to this allergen found in soy flour. The infinitesimal quantity of proteins in soybean oil very probably explains the negativity of the prick test for the oil. The reaction may also have been promoted at a minimal dose by the coexistence of an angiotensin receptor antagonist and a beta-blocker. These drugs are known risk factors for food-related anaphylactic reactions (31,32).

## Conclusion

Although rare, peranaesthetic allergic accidents imputable to the propofol excipient are likely to occur in patients allergic to birch

pollen or soy, because of the presence of residual allergenic proteins in soybean oil, even refined. The reactogenic quantity of soy protein given intravenously is not known. Although the residual quantity in the oil is very small, its role in triggering an allergic reaction cannot be denied. The fact that the product is injected intravenously, particularly in asthmatic children and those allergic to soy, may explain the observed incidents, particularly the severity of the bronchospasm. As the sensitization to pollens indicates atopy, and consequently is a risk factor for further sensitization to other food proteins such as soy residual proteins in soy oil, it therefore seems essential for the pre-anaesthetic interview to look for a pollinosis, and a food allergy to soy, because cross-reactivity is common (33). In the event of anaphylaxis, a test for sensitization to birch pollen and to soy should be carried out. Assertions that refined soybean oil no longer contains proteins must be subjected to critical reassessment. The pharmaceutical industry should provide a regular check of batches of soybean oil used in the manufacture of intravenous drugs such as propofol and parenteral nutrition products.

### Conflict of Interest

Christelle Richard and Sandrine Jacquenet were employed by Genclis.

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