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Anaphylaxis Due to Propofol

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Propofol is an alkyl phenol in a lipid vehicle. When it was first introduced in Europe, the vehicle was Cremophor EL, but a high incidence of anaphylactic reactions prompted the change to a fatty emulsion containing soybean oil, egg lecithin (phosphatide), and glycerol, which reportedly is not associated with histamine release.[1,2]

Anaphylactic shock has been reported in the European literature after first exposure to propofol.[3,4] We are reporting a case of anaphylaxis after a third anesthetic induction with propofol. To our knowledge, this is the first case report of anaphylaxis after reexposure to propofol.

CASE REPORT

A 62-yr-old, 76-kg, 170-cm woman was admitted to Roswell Park Cancer Institute with a diagnosis of left ureteral obstructive uropathy with stricture of the ileourethral anastomosis. Her past history included transitional cell carcinoma of the urinary bladder with invasion of the pelvic lymph nodes, for which she underwent a radical cystectomy with pelvic node dissection and ileal-conduit creation. She also received chemotherapy with methotrexate, vincristine, doxorubicin, and *cis*-platinum. Her hypertension was well controlled with diltiazem 60 mg orally three times daily and clonidine 0.1 mg orally twice daily. She also underwent a cystoscopy and left ureteral stent placement before having the radical cystectomy. During both procedures, performed 6 months before this admission, 100 mg propofol was used for each induction of general anesthesia without any side effects. She denied any allergies. Physical examination, laboratory results, ECG, chest x-ray, and lung spirometry were all normal. Two dimensional echocardiography revealed normal chamber sizes, normal valves, and a left ventricular ejection fraction of 55%.

The patient was scheduled for a left ureteral stent and ileal conduit revision and received diazepam 10 mg, clonidine 0.1 mg, and diltiazem 60 mg 1 h before surgery. Upon arrival to the operating room, standard monitoring was applied, including both central venous and intraarterial catheters. Initial central venous pressure (CVP) was 5 mmHg and initial arterial pressure 120/70 mmHg. A bolus of 500 ml lactated Ringer's solution was then administered, resulting in an increase of CVP to 8 mmHg.

A single-orifice epidural catheter was easily inserted in the T9–T10 intervertebral space, and a test dose of 1.5% lidocaine with epinephrine 1:200,000 (3 ml) was given without an increase in heart rate or signs of spinal blockade. No other medications were administered into the epidural space.

General anesthesia was induced with propofol 50 mg, vecuronium 9 mg (4 min after a priming dose of 0.7 mg), and sufentanil 50 μg intravenously, without significant changes in blood pressure or heart rate. Following tracheal intubation, anesthesia was maintained with 0.2% isoflurane and 50% oxygen/air.

Five minutes after induction of general anesthesia, the blood pressure decreased to 70/50 mmHg with a junctional rhythm of 130 beats per min. Isoflurane was discontinued; the patient was placed in Trendelenburg's position; and 500 ml lactated Ringer's solution and 500 ml 6% hetastarch were administered because the CVP had decreased to 4 mmHg. Incremental doses of ephedrine were also administered (5 mg × 4 in 10 min). The blood pressure increased to 90/60 mmHg; the CVP increased to 10 mmHg; and the heart rhythm converted to sinus tachycardia. Five minutes later the blood pressure was 60/40 mmHg with a heart rate of 130 beats per min. A pulmonary artery catheter was then inserted while a dopamine infusion was started at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 1 g of calcium chloride was infused over 3 min, to rule out the possibility of hypotension due to calcium channel blockade. The dopamine infusion was titrated up to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to maintain the systolic blood pressure between 90–100 mmHg. Right side heart catheterization opening pressures were right atrium = 4 mmHg, right ventricle = 45/2 mmHg, pulmonary artery pressure = 45/5 mmHg, and pulmonary artery occlusion pressure = 4 mmHg. Cardiac output was 10.95 $l \cdot min^{-1}$, and systemic vascular resistance was 410 $dyn \cdot s^{-1} \cdot cm^{-5}$. A hyperdynamic state due to thyrotoxicosis, malignant hyperthermia, or fulminant sepsis were ruled out, and anaphylaxis was suspected. As the surgical drapes were removed, severe edema and skin wheals were found on the right thorax and arm where the drugs had been administered. Also, severe edema of the right ear lobe and neck were noted. Generalized erythema was also present. No auscultatory signs of bronchospasm were heard; the peak inspiratory pressures were between 38–40 cmH_2O; and the oxyhemoglobin saturation remained around 98% on 100% FI_{O_2} throughout the event. Diphenhydramine 50 mg and hydrocortisone 100 mg were then administered intravenously. Within 10 min the blood pressure started to increase from 100/60 to 150/85 mmHg. The dopamine infusion was slowly discontinued over a 15-min interval. The generalized erythema disappeared but the edema on the right upper side of the body remained for 24 h. The trachea was extubated 6 h later in the intensive care unit when the patient was fully awake and hemodynamically stable, and after fiberoptic laryngoscopy and bronchoscopy had shown no significant edema of the upper airway. Myocardial infarction was ruled out on the basis of negative ECG and enzyme criteria. The patient was transferred out of the surgical intensive care unit 24 h after the event and discharged home 48 h later. Blood samples for plasma levels of immunoglobulin E (IgE) antibody and complement C_3 and C_4 protein fraction were drawn 1 and 6 h after the event. Reported values were IgE antibody 10 $ng \cdot ml^{-1}$ and 600 $ng \cdot ml^{-1}$ respectively (normal values less than 250 $ng \cdot ml^{-1}$). Reported values for complement were C_3 fraction 800 and 400 $\mu g \cdot ml^{-1}$ (normal value 1200 $\mu g \cdot ml^{-1}$) and C_4

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fraction 300 and 180 $\mu g \cdot ml^{-1}$ (normal value 450 $\mu g \cdot ml^{-1}$), respectively.

The patient underwent skin testing 4 days after the event. Skin tests with dilutions of propofol, vecuronium, sufentanil, diazepam, clonidine, and diltiazem showed an immediate reaction for propofol only (table 1). Additional skin tests were performed with the lipid vehicle (10% Intralipid) and phenol. Immediate reaction was seen when tested with phenol. She was informed of the results and of the risk for anaphylaxis if reexposed to propofol or phenol in the future.

TABLE 1. Results of Skin Testing

Drug	Concentration 1:10 Prick Test Reaction	Concentration 1:100 Intradermal Reaction	Wheal (mm)	Flare (mm)
Saline	−	—	0	0
Histamine	+	Not tested*	1	3
Sufentanil	−	—	0	0
Vecuronium	−	—	0	0
Propofol	+++	Not tested*	5	10
Intralipid 10%	−	—	0	0
Phenol	+++	Not tested*	5	10

+ = mild reaction; +++ = severe reaction; − = no reaction.
* Intradermal reaction not tested due to degree of reaction with prick test.

DISCUSSION

The new formulation of propofol was thought to be nonallergenic.[1,2] Fahmy *et al.* reported that serum histamine levels were unchanged after an induction dose of either propofol or thiopental.§ Nevertheless, reports have documented anaphylactic reactions (particularly when used in combination with atracurium),[5] local histamine release,[6] delayed type I allergic reactions,[7] and anaphylaxis.[3]

The new vehicle for propofol contains highly purified egg phosphatide, extracted from egg yolk. This phosphatide compound is different from egg albumin, which is found in the egg white to which most patients with egg allergies react. In guinea pigs sensitized by a single intraperitoneal injection to egg albumin or propofol, anaphylaxis was not detected when they received an intravenous bolus injection of propofol.¶

Propofol (2,6-diisopropyl-phenol) has two potential allergenic molecules: the diisopropyl side chain and phenol. Our patient showed a definite skin response to a low concentration of phenol, which we believe may have developed during the second administration of propofol. However, other patients who develop anaphylaxis after a first exposure may do so because of a sensitivity to the diisopropyl radical, which is found in many dermatologic products.** Since skin testing prior to propofol administration is not economically practical, a thorough history of sensitivities to dermatologic products or phenol, as well as the prior use of parenteral nutrition with Intralipid, is important. In addition to a positive history of allergies, the number of exposures to the same or different but chemically related drugs can influence the incidence of allergic reactions.[8] Our patient had no history of allergies, but her anaphylactic reaction exemplifies that sensitization can also occur in normal patients.

The interval between exposures and the route of administration is also important in the development and expression of drug allergy. A 2-week interval is apparently needed for these phenomena to occur.[9] Anaphylaxis is also more likely to occur after intravenous than after intramuscular injection of a drug.[8] A history of prior exposure to a drug without untoward effects does not rule out the possibility of anaphylaxis.

The marked increase of circulating IgE antibodies 6 h after the event suggests the occurrence of an anaphylactic reaction. Concomitant decreases in C_3 and C_4 complement fractions may or may not corroborate the diagnosis. If the reaction is IgE mediated, then the complement should remain unchanged despite the alterations in IgE antibodies. The decrease in complement levels in this patient suggest hemodilution, due in part perhaps to rapid volume administration. Skin testing (intradermal testing of serial dilutions from 10^{-3} to 10^{-1}), the IgE inhibition test, leukocyte histamine release test, human basophil degranulation test, and radioallergosorbent test all can be used to determine which drug triggered the anaphylactic response.[3,8] This patient underwent intradermal testing, which proved to be highly positive for propofol. Further testing with phenol and the surfactant (10% intralipid) showed a definite reaction to phenol (table 1). It is important to determine which component of the drug is triggering the reaction so that potential responses may be avoided, since many drugs have the same chemicals in their structure.

In conclusion, a case of IgE-mediated anaphylaxis due to repeated propofol injections is presented. Despite a lack of history of allergies, the increase use of propofol may result in more cases such as the one described.

Finally, the authors suggest that in any case of unexplained severe hypotension or death following the administration of intravenous drugs, a collection of 10 ml blood should be done before or shortly after death. The diagnosis of anaphylaxis can be made even *post mortem* by radioimmunoassay for drug-specific IgE antibodies and may help to determine the cause of death.[10] While there is not radioallergosorbent test available for propofol at

§ Fahmy NR, Alkhouli HM, Mefford I, Caliguri E, Durkin T: Hemodynamics, histamine release and plasma cathecolamines following anesthetic induction with propofol or thiopental (abstract). ANESTHESIOLOGY 65:A360, 1986.

¶ ICI Americas Inc.: Data on file. Wilmington, Delaware.

** Mouton C, Mata E, Gerard P, Gueant JL, Laxenaire MC: Premier cas de choc anaphylactique au propofol, agent anesthesique recent. Annales Medicales de Nancy et de l'Est 29:47, 1990.

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this time, it has been used to diagnose fatal reactions to penicillin, muscle relaxants,[11] and thiopental.[12]

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Kartagener's Syndrome: Anesthetic Considerations

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Kartagener's Syndrome is a rare disorder characterized by situs inversus, including dextrocardia, and primary ciliary dyskinesia resulting in chronic respiratory tract infections, bronchiectasis, and sinusitis.[1]

We present, to our knowledge, the first recorded case in the English literature of anesthetic management of a patient with Kartagener's Syndrome.

Case Report

A 68-yr-old woman was admitted to the hospital for bleeding colonic polyps and gingiva. The patient was diagnosed as having Kartagener's Syndrome; this diagnosis was based in part on clinical findings of situs inversus, including dextrocardia, recurrent respiratory infection, bilateral predominantly basal bronchiectasis, chronic ear infections, and occasionally, bronchospasm. She had a history of recurrent atrial fibrillation, hypertension, and diabetes mellitus and was receiving Coumadin, diltiazem, and captopril. She had a cough productive of yellowish phlegm. Chest examination revealed rales at both lung bases and diffuse bronchospasm. Her admission coagulation profile was abnormal (international normalized ratio 3.7, activated partial thromboplastin time 55 s). The preoperative electrocardiogram done with leads normally placed showed abnormal limb and precordial leads (fig. 1A). A normal ECG emerged when all the leads were reversed (fig. 1B). Spirometry showed a moderate obstructive pattern. The chest x-ray revealed cystic bronchiectasis at both lung bases and dextrocardia.

The patient received vitamin K and several days of chest physiotherapy and bronchodilator and antibiotic treatment before undergoing resection of what then was revealed to be an adenocarcinoma of the colon.

Premedication consisted of oxazepam, morphine, and scopolamine. Before the induction of anesthesia, a lumbar epidural catheter was placed for postoperative pain management. A radial arterial monitor was inserted. A central venous catheter was placed in the left internal jugular vein, according to the assumption that the great vessels and the thoracic duct were mirror images of normal. Despite the patient's prominent front teeth and a mild micrognathia, visualization of the larynx was not difficult during awake laryngoscopy under topical anesthesia. Anesthesia then was induced, and the patient's trachea was intubated and her lungs mechanically ventilated. The humidification of the inspired gases was maintained with a heat and humidity exchanger (Thermovent®). Bronchoscopy was performed and showed that the tracheal and bronchial mucosa were grossly normal. The left main stem bronchus was found to be slightly more in the caudad-cephalad direction than on the right. The first lobar bronchus on the left main was at about 2–3 cm from the carina, and the first lobar bronchus

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