

Type I Hypersensitivity in an Asthmatic Child Allergic to Peanuts: Was Soy Lecithin to Blame?

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Background: Soy lecithin is widely used as an emulsifier, not only in topical skin care products but also in various drugs administered either topically, orally, or intravenously or by inhalation. Patients strongly allergic to soy and/or peanuts can develop an anaphylactic reaction when exposed to soy lecithin.

Method: We report a 3-year-old asthmatic boy, allergic to peanuts, who was treated at the emergency department for an exacerbation of asthma following an upper respiratory tract infection. Within an hour after receiving the second of two inhalations of an ipratropium bromide (Atrovent) metered dose inhaler, he developed respiratory distress and generalized urticaria, an adverse event that regressed within 48 hours of withdrawal of the suspected drug. Soy lecithin, contained as an excipient in the metered dose inhaler, was strongly suspected of being responsible for this reaction.

Conclusion: Drug products containing soy lecithin can cause severe allergic reactions in patients allergic to peanuts or soy. Physicians should be aware that adverse drug reactions can be due to both the active medical component and the excipient ingredients.

Antécédents: L'utilisation de la lécithine de soya comme émulsifiant est répandue, non seulement dans les produits de soins de beauté mais également dans divers médicaments appliqués de façon topique, orale, intraveineuse, ou par inhalation. Les patients fortement allergiques au soya, aux arachides, ou aux deux peuvent développer une réaction anaphylactique lorsqu'ils sont en contact avec la lécithine de soya.

Objectif: Rapporter le cas d'un enfant asthmatique de 3 ans, allergique aux arachides, qui a été traité au service d'urgence pour une poussée d'asthme à la suite d'une infection des voies respiratoires supérieures.

Résultat: Au cours de l'heure qui a suivi la deuxième de deux inhalations au bromure d'ipratropium en aérosol doseur (Atrovent), l'enfant est tombé en détresse respiratoire et a développé une urticaire généralisée, un effet secondaire qui s'est résorbé 48 heures après la discontinuation du médicament en cause. La lécithine de soya, qui se trouve comme excipient dans le bromure d'ipratropium en aérosol doseur (Atrovent), est la principale composante mise en cause dans cette réaction.

Conclusion: Les médicaments qui contiennent de la lécithine peuvent causer des réactions chez les patients allergiques aux arachides et au soya. Les médecins devront être conscients que les réactions aux médicaments peuvent être causées aussi bien par les principes actifs que par les ingrédients excipients.

A 3-YEAR-OLD BOY with preexisting asthma was transferred to Sainte-Justine Hospital, a pediatric tertiary care center in Montreal, with bronchospasm and dyspnea. The initial vital signs were as follows: temperature

38.6°C, pulse 172 beats per minute, respiratory rate 56 breaths per minute, blood pressure 105/57 mm Hg, O₂ saturation 90%, weight 16 kg, and height 100 cm. Respiratory distress with wheezing, tachypnea, and increased coughing, in spite of two treatments of salbutamol (Ventolin) given at close intervals, was observed on his arrival at the emergency room. A cutaneous examination revealed moderate atopic eczema for which he had been treated with hydrocortisone 1% (Cortoderm).

The patient was born at 35 weeks of gestation by induced vaginal delivery because of premature rupture of membranes. His birth weight was 2 kg, and his height was 44 cm (20th percentile for weight and height for a 35-week

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preterm neonate). He was breast-fed exclusively for 3 months. Cereals, fruits, and vegetables were introduced to the diet without problems. Homogenized milk replaced formula milk at the age of 12 months. The patient had an anaphylactic reaction at 10 months of age after an accidental ingestion of peanut butter and developed asthma at 18 months of age. He had no history of an adverse reaction to medications or vaccinations and had never been hospitalized.

The family history revealed that the mother had received oral amoxicillin for treatment of cystitis in the fourth month of pregnancy. The mother was allergic to coconut (urticaria) and had asthma from the age of 10 years. She had eaten peanut butter several times a week throughout the course of her pregnancy but none while breast-feeding. She did not consume nuts or soy products, neither during pregnancy nor while breast-feeding. The father had no history of allergies.

At home, asthma medication consisted of fluticasone (Flovent) 50 µg inhalations twice a day and salbutamol (Ventolin) 200 µg inhalations every 4 hours as needed. The day before his hospitalization, he showed signs and symptoms of upper respiratory tract infection for which salbutamol (Ventolin) was administered. In spite of this medication, his condition deteriorated, which prompted the parents to bring him to the emergency department, where he received prednisone 15 mg orally (1 mg/kg) and three salbutamol (Ventolin) treatments of 500 µg at 30-minute intervals. Ipratropium bromide (Atrovent) metered dose inhaler 250 µg was added as there was no significant improvement in the bronchospasm. The patient received this combination of salbutamol and ipratropium bromide twice over an hour. An hour following the second dose of ipratropium bromide (Atrovent), he developed generalized urticaria associated with acute respiratory distress with tachypnea at 48 respirations per minute and a need for oxygen supplementation in light of O₂ saturation that dropped to 40%. Ipratropium bromide was stopped, and diphenylhydramine (Benadryl) was prescribed at 24 mg orally every 6 hours for itching. Following cessation of the ipratropium bromide metered dose inhaler, oxygen supplementation, and administration of three doses of diphenylhydramine and 15 mg of prednisone, the acute respiratory distress resolved, the pruritus disappeared, and the eruption progressively subsided within 48 hours. The patient was discharged after 4 days of hospitalization with prednisolone (Pediapred), salbutamol (Ventolin), and fluticasone propionate (Flovent). There was no history of accidental peanut ingestion, neither at home prior to his visit to the

hospital nor at the emergency department. The patient was lost to follow-up, so confirmation of soy allergy through rechallenge or skin-prick testing was impossible.

Discussion

Ipratropium bromide (Atrovent, a quaternary ammonium derived from atropine) is used in asthmatic patients in combination with β_2 -stimulating medications, such as salbutamol (Ventolin), to increase their bronchodilator effect. The formulation of the ipratropium bromide (Atrovent) metered dose inhaler contains soy lecithin as an excipient (as opposed to ipratropium bromide inhalation solution and salbutamol [Ventolin], which does not contain soy lecithin).

The compatibility (responsibility of a drug for an adverse reaction) according to the method¹⁻³ used in pharmacosurveillance at our hospital demonstrated a 92% probability that the anaphylactic reaction was due to the soy lecithin contained in the ipratropium bromide metered dose inhaler. Our patient had a known severe allergy to peanuts. It has been reported that exposure to peanuts in utero, especially if the mother had consumed peanuts more than twice weekly, can sensitize the fetus to peanuts. Also, several studies have shown that breast-feeding does not protect the child from possible sensitization to peanut allergens,⁴ and sensitization to peanuts has also been reported through breast-feeding.⁵⁻⁷

Soybean and peanut are members of the legume family and share several common antigenic fractions. Severe food allergies caused by soy protein in asthmatic children and adolescents allergic to peanuts have also been reported.⁸ There have even been reports of death secondary to anaphylaxis owing to soy exposure in asthmatics known to be anaphylactic with respect to peanuts.⁹ A previous case of allergy to soy lecithin contained in the ipratropium bromide (Atrovent) metered dose inhaler has been reported.¹⁰ This 40-year-old woman, with long-standing asthma and a severe allergy to soybeans, developed wheezing, laryngospasm, and generalized pruritus, which required subcutaneous epinephrine administration. It was unclear whether she was allergic to peanuts.¹⁰ Another 32-year-old woman with chronic asthma developed an anaphylactic shock within minutes of taking ipratropium bromide (Atrovent) inhalation aerosol.¹¹ She had no known drug allergies but did have an allergy to peanuts. It was concluded that the anaphylactic reaction was due to the soy lecithin in the newly prescribed inhaler. A third female asthmatic patient developed paradoxical bronchospasm, laryngospasm, and cutaneous rash after metered-

dose inhaled bronchodilators containing soy-derived excipients.¹² This patient was not allergic to soy, as was demonstrated by negative skin tests against soy lecithin and negative radioallergosorbent test against soy, and her pseudoallergic systemic reaction was explained by intolerance to soy lecithin as a consequence of an "irritant" effect of such compounds.

Low birth weight and maternal infection during pregnancy have been reported as risk factors that may increase the risk for atopy in children.^{13,14} Both factors were present in the history of our patient.

Soy lecithin consists of phospholipids extracted from soybean oil. It is widely used as a natural emulsifier in processed foods, pharmaceuticals, and cosmetics and is used as a vehicle for molecules with limited solubility. It is found in aerosol preparations for inhalation (eg, ipratropium bromide [Atrovent], ipratropium bromide and salbutamol [Combivent]), in liposomal formulations of injectable preparations (eg, liposomal amphotericin B or AmBisome), and as an ingredient of pills and suppositories. Liposomal preparations for amikacin, ciprofloxacin, foscarnet, doxorubicin, nystatin, and naproxen, among others, are being evaluated. Liposomes are biodegradable lipid particles that carry a drug to its site of action, thus decreasing the risk of systemic toxicity. Soy lecithin is preferred over egg yolk, traditionally used in liposomal preparations, because of its greater affinity for the liver and kidneys, as demonstrated in studies using interferon.¹⁵ Incorporation of soy lecithin in ophthalmic preparations in emulsion form may prolong the activity of pilocarpine.¹⁶ In dermatology and cosmetology, soy lecithin enhances percutaneous penetration.¹⁷

A severe allergic reaction manifested by generalized urticaria and pruritus was reported in a 2-year-old girl after administration of a soy lecithin containing liposomal formulation of amphotericin B (AmBisome).¹⁸ Severe allergies and anaphylaxis related to liposomal amphotericin B (AmBisome) have also been reported in adult patients.^{19–21} Subsequently, the child and two adult patients received conventional intravenous amphotericin without any allergic reaction. It was not mentioned, however, whether these individuals were allergic to soy or peanuts.^{18–21}

The major allergens responsible for type I hypersensitivity to soy are glycoproteins found in the hulls and dust of the soybean. In our cases, as in other reported cases,^{22,23} a type I hypersensitivity may well have been due to soy protein contaminants remaining despite chemical processing of soy lecithin, a process using a hot solvent extraction technique that eliminates most allergenic proteins.

Another possibility is a pseudoallergic systemic reaction owing to an "irritant" effect of the excipient.¹²

In January 2006, the European Medicines Agency for Evaluation of Medicines for Human Use concluded that although relevant type I reactions have been reported only after intravenous infusion of major quantities of soybean oil, soya and peanut products should be treated as allergenic. The agency proposed that warnings be added to package leaflets of products containing soy lecithin administered intravenously, rectally, or by inhalation as follows: "Medicinal product contains soya lecithin. If you are allergic to soya or peanut, do not use this medicinal product."²⁴ In April 2006, the US Food and Drug Administration also released their guidelines for labeling of certain products using lecithin derived from soy.²⁵ Following these recommendations, some drug manufacturers have modified or are in the process of modifying the monography of their peanut or soy extract-containing products.

Conclusion

The occurrence of adverse reactions to drug excipients is rare, but it can be life-threatening. The cause of these cutaneous or respiratory reactions may be difficult to diagnose because clinicians often overlook the possible role of nonmedicinal ingredients of a suspected drug.

Food-allergic patients depend on crucial product information. Although rare, soy lecithin allergenicity has been documented. Until the details of this reaction are better characterized in the medical literature through further reports, patients with allergies to soybean or peanut are being advised against exposure to soy lecithin.

References

1. Goodman N. Toward evidence-based medical statistics 2: the Bayes factor. *Ann Intern Med* 1999;130:1005–13.
2. Bate A, Lindquist M, Edwards IR, et al. A bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol* 1998;54:315–21.
3. Auriche M. Approche bayésienne de l'imputabilité des phénomènes indésirables aux médicaments. *Thérapie* 1985;40:301–6.
4. Frank L, Marian A, Visser M, et al. Exposure to peanuts in utero and in infancy: the development of sensitization to peanut allergens in young children. *Pediatr Allergy Immunol* 1999;10:27–32.
5. Hourihane JO, Dean TP, Warner JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. *Br Med J* 1996;313:518–21.
6. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics* 1998;102:E8.

7. Ewan PW. Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations. *Br Med J* 1996;312:1074–8.
8. Foucard T, Edberg U, Malmheden Yman I. Fatal and severe food hypersensitivity. Peanut and soya underestimated allergens. *Lakartidningen* 1997;94:2635–8.
9. Foucard T, Malmheden Yman I. A study on severe food reactions in Sweden—is soy protein an underestimated cause of food anaphylaxis? *Allergy* 1999;54:261–5.
10. Fine SR. Possible reactions to soya lecithin in aerosols. *J Allergy Clin Immunol* 1991;87:600.
11. Karch AM, Karch FE. It was a shock. *Am J Nurs* 2003;103:27.
12. Facchini G, Antonicelli L, Cinti B, et al. Paradoxical bronchospasm and cutaneous rash after metered-dose inhaled bronchodilators. *Monaldi Arch Chest Dis* 1996;51:201–3.
13. Steffensen FH, Sorensen HT, Gillman MW. Low birth weight and preterm delivery as risk factors for asthma and atopic dermatitis in young adult males. *Epidemiology* 2000;11:185–8.
14. Xu B, Jarvellin MR, Pekkanen J. Prenatal factors and occurrence of rhinitis and eczema among offspring. *Allergy* 1999;54:829–36.
15. Kalenik TN, Motavkina NS, Vorob'ev AA. Liposome-incorporated interferon. The design of liposomal interferon. *Zh Mikrobiol Epidemiol Immunobiol* 1999;3:55–8.
16. Zurowska-Pryczkowska K, Sznitowska M, Janicki S. Studies on the effect of pilocarpine incorporation into a submicron emulsion on the stability of the drug and the vehicle. *Eur J Pharm Biopharm* 1999;47:255–60.
17. Valenta C, Wanka M, Heidlas J. Evaluation of novel soya-lecithin formulation for dermal use containing ketoprofen as a model drug. *J Control Release* 2000;63:165–73.
18. Cesaro S, Calore E, Messina C, Zanesco L. Allergic reaction to the liposomal component of liposomal amphotericin B. *Support Care Cancer* 1999;7:284–6.
19. Schneider P, Klein RM, Dietze L, et al. Anaphylactic reaction to liposomal amphotericin B [letter]. *Br J Haematol* 1998;102:1108–9.
20. Laing RBS, Milne LJR, Leen CLS, et al. Anaphylactic reactions to liposomal amphotericin [letter]. *Lancet* 1994;344:682.
21. Ringden O, Andström E, Remberger M, et al. Allergic reactions and other rare side-effects of liposomal amphotericin [letter]. *Lancet* 1994;344:1156–7.
22. Awazuhara H, Kawai H, Baba M, et al. Antigenicity of the proteins in soy lecithin and soy oil in soybean allergy. *Clin Exp Allergy* 1998;28:1559–64.
23. Renaud C, Cardiet C, Dupont C. Allergy to soy lecithin in a child. *J Pediatr Gastroenterol Nutr* 1996;22:1559–64.
24. European Medicines Agency for Evaluation of Medicines for Human Use, Committee on Herbal Medicinal Products. Public statement on the allergenic potency of herbal medicinal products containing soya or peanut protein. London, 12 January 2006. Doc Ref: EMEA/HMPC/138139/2005. Available at: www.emea.eu.int/pdfs/human/hmpc/13813905en.pdf.
25. Guidance for Industry. Guidance on the labeling of certain uses of lecithin derived from soy under section 403(w) of the federal Food, Drug, and Cosmetic Act. CFSAN/Office of Food Additive Safety; April 2006.

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