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Anaphylaxis in a Milk-Allergic Child After Ingestion of Soy Formula Cross-contaminated With Cow's Milk Protein

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ABSTRACT. In this report we describe a 9-month-old boy with severe persistent asthma and documented cow's milk allergy (presented with eczema and severe systemic reactions) who had an anaphylactic reaction to a soy formula contaminated with cow's milk protein. Quantitative enzyme-linked immunosorbent assay analysis revealed trace quantities of β -lactoglobulin in the offending soy formula as well as the dry powder. The patient did not demonstrate clinical reactivity to soy protein (negative challenge, tolerated pure soy formula well). Cross-contamination of the offending soy formula was presumed to have occurred during food manufacturing. This case demonstrates that trace quantities of cow's milk protein can elicit severe systemic reactions in highly milk-allergic individuals. This infant ingested the equivalent of 0.4 mL of cow's milk from the soy formula as documented by an immunoassay for β -lactoglobulin. This highlights the ease with which cross-contamination can occur during food processing and reinforces the need for better quality control. *Pediatrics* 2005;116:1223–1225; anaphylaxis, food allergy, cross-contamination.

ABBREVIATION. IgE, immunoglobulin E.

Cow's milk is one of the first foreign proteins ingested by infants and is one of the most common food allergens, affecting ~2.5% of infants and young children. Anaphylaxis is the most serious manifestation of food allergy. Patients with underlying severe or uncontrolled asthma who experience anaphylaxis after food ingestion constitute a high-risk group for fatal reactions to food allergens.

The presence of cow's milk is widespread in foods and is often included as an unlabeled ingredient or because of cross-contamination (major source of hidden allergens). Examples of cross-contamination include those caused by processing errors (eg, ingredients added to food by mistake) and processing on

shared lines (where the equipment is not adequately cleaned or leftover products are used or "reworked" to the next batch of products). Contact of 1 food with another even in trace amounts can pose a problem for a highly allergic individual.

CASE REPORT

E.M. is a 9-month-old boy who was first seen by the allergy clinic of the Red Cross War Memorial Children's Hospital at the age of 6 months with asthma, eczema, and food allergies. He had been experiencing difficulty breathing about once a week and was responsive to short-acting β_2 agonists given via nebulizer or metered-dose inhaler. He had experienced severe systemic reactions to cow's milk and custard (exacerbations of asthma, vomiting, and an urticarial rash) but had been tolerating (and experiencing no adverse reactions to) soy formula as a supplement to the mother's breast milk.

On examination he had features of atopy and asthma with allergic shiners, Denny-Morgan lines, and reversible lower airway obstruction. He was commenced on budesonide, 200 μ g twice daily via metered-dose inhaler, and prednisone was given orally for 3 days. Skin-prick tests for inhalant allergens (ALK-Abello, Hoersholm, Denmark) were positive for dog (wheal, 4 mm; flare, 6 mm) and negative for cat, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cockroach, molds, and grasses. Histamine dihydrochloride was used as a positive control and saline as a negative control. A positive test was regarded as a wheal read 15 minutes after testing with a diameter of >3 mm larger than the negative control.

After 1 month the eczema was flaring acutely, and the food allergies were explored further because he had experienced additional reactions to cow's milk-containing products. Skin-prick tests (see Table 1) were deemed positive for cow's milk, egg white, peanut, potato, wheat, and soy according to the commonly used grading method, with which a positive skin test is regarded as a mean wheal diameter of 3 mm greater than the negative control. ImmunoCAP tests (CAP-System, Pharmacia Diagnostics AB, Uppsala, Sweden) were positive for cow's milk, egg white, potato, peanut, wheat, and soy according to manufacturer guidelines (see Table 1).

Interpretation of the skin-prick tests results¹ suggested a high positive predictive value for food allergy to milk, egg white, peanut, and wheat. However, according to a recent report² on the clinical significance of food-specific immunoglobulin E (IgE) values, only the increased values for milk and egg white are associated with a high positive predictive value for a food reaction, the values for peanut and potato lie in the high but nonpredictive range, and the values for wheat and soy predict a low chance of clinical reactivity.

Egg, milk, potatoes, and peanuts were eliminated from the diet with the aid of a dietician, who recommended alternative nutrient sources to ensure nutritional adequacy of the diet. E.M. had continued breastfeeding (without manipulation of the maternal diet) and continued to tolerate soy formula. After 1 month, the eczema had improved markedly but he had had 2 acute attacks of asthma that required nebulization and 5 days of prednisone. His mother's adherence and inhaler technique were checked and found to be good. Salmeterol, 25 μ g twice daily, was added to his twice-daily 200- μ g budesonide dose as controller treatment.

At the age of 9 months, E.M.'s mother tried a new brand of soy

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TABLE 1. Investigations at 7 Months of Age

Food	Skin-Prick Tests		ImmunoCAP, kU/L
	Wheal, mm	Flare, mm	
Milk	10	15	43.0
Casein	ND	ND	40.7
Egg white	10	20	7.6
Peanut	6	10	4.1
Potato	6	10	9.6
Wheat	3	6	1.0
Soy	3	6	0.79
Fish	1	NR	<0.35
Maize	NR	NR	<0.35
Negative control	NR	NR	NA
Positive control	7	12	NA

ND indicates not done; NA, not applicable; NR, no reaction.

formula, of which he ingested ~50 mL. After half an hour he vomited, stopped breathing, and became cyanotic. A neighbor performed mouth-to-mouth resuscitation, to which he responded promptly, and he was transported by ambulance to hospital. On arrival at the hospital he was wheezing loudly and an urticarial rash was evident. He was treated with epinephrine intramuscularly, hydrocortisone intravenously, and oral prednisone, and he was nebulized with salbutamol. His serum tryptase level (18 hours after the reaction) was 2.7 $\mu\text{g/L}$, and ImmunoCAP tests were repeated. His parents were trained in cardiopulmonary resuscitation and intramuscular administration of epinephrine.

Samples of the brand of soy formula (the mixed soy formula in his own bottle, the unmixed soy powder, and a sample of the same manufacturer's soy powder from a different batch) were analyzed for β -lactoglobulin, egg white protein, and peanut protein (see Table 2) (RIDASCREEN enzyme-linked immunosorbent assay; R-Biopharm, Darmstadt, Germany). Milk proteins ($32.4 \text{ mg} \cdot \text{L}^{-1}$) were found in the bottle containing the soy formula, as well as in the batch of dry soy powder ($196.2 \text{ mg} \cdot \text{kg}^{-1}$) that was used to mix this formula.

To compare these concentrations and exclude the possibility of additional contamination of the child's bottle with milk from another source, we converted the concentration of milk protein found in the mixed formula to that in the dry soy powder (assuming that the mother mixed the formula and water according to the manufacturer's instructions with 4 g of powder per 25 mL of water [160 g of powder per liter of water]). The concentrations were almost identical in the mixed formula in the bottle and the dry powder from the same batch with 202.5 and $196.2 \text{ mg} \cdot \text{kg}^{-1}$, respectively. Analysis of a different batch from the same brand did not detect any milk residues. No egg or peanut proteins were found in any of the samples.

The repeat ImmunoCAP tests revealed specific IgE levels of 72.5 kU/L to milk and 2.3 kU/L to soy, which are strongly increased compared with the initial analysis (see Table 1). Open oral challenge to soy (using the brand that he had previously tolerated) was performed 10 days later when he was fully recovered. During this challenge he ingested a total of 113 mL of soy formula with no ill effects.

DISCUSSION

Although allergic persons can react to foods containing trace quantities of food allergens, there are

few data available on the quantities of these allergens required to evoke allergic symptoms. We report on a 9-month-old boy with asthma, eczema, and cow's milk-induced wheezing who experienced anaphylaxis and respiratory arrest after the ingestion of trace quantities of β -lactoglobulin that were found to be contaminating a dry-powder soy formula.

Because soy protein formula is a substitute feed in IgE-mediated cow's milk allergy, it is critical that such products conform to high standards of purity and that cross-contamination with milk protein is avoided. Lack of uniformity in the literature of the methods of analysis for milk makes it difficult to compare this result to previous reports of cross-contamination. Threshold doses required for clinical reactivity to cow's milk differ from patient to patient, with 5% of patients reacting to <30 mg of milk protein and 1% reacting to <1 mg.³ However, threshold doses required for clinical reactivity to cow's milk protein may be as low as 0.1 mL of milk,⁴ and case reports of patients experiencing reactions to cow's milk because of contamination of nondairy foods bring the threshold level for reactivity down even further to 120 to 180 μg of whey protein (equivalent to ~23–24 μL of milk).⁵ A statistical model estimating the threshold dose for clinical reactivity in 1 in 1 million susceptible patients places the dose at 0.005 mg of cow's milk.⁶

Previous studies quantified various protein constituents of cow's milk with assays of differing sensitivities, which makes it difficult to convert these data into estimated quantities of whole milk. An international consensus protocol⁷ has been developed to use standardized food challenges to establish the threshold doses of foods with a 95% certainty that 90% of food-allergic individuals will not react to that dose. The protocol addresses the issues of the standardization of the allergen content of challenge foods. We report on a child who ingested ~1.6 mg of β -lactoglobulin. It is estimated that the total protein content of cow's milk is up to 35 mg/L, and ~10% of this is β -lactoglobulin.⁸ Therefore, the child reacted to the equivalent of milk allergen present in ~0.4 mL of whole cow's milk.

Because of complex terminology being used for food labeling, the majority of parents are currently unable to identify common allergenic food ingredients, with this problem being more marked for milk- and soy-containing products than for peanut-containing products.⁹ This leads to a risk of clinical reactions.¹⁰ Recently, however, considerable pres-

TABLE 2. Concentrations of Various Allergens in Samples

Allergen	Soy Formula in Child's Own Bottle	Dry Soy Powder Used to Mix the Formula That Caused Anaphylaxis	Dry Soy Powder (Same Brand but Different Batch)
β -lactoglobulins (milk), $\text{mg} \cdot \text{kg}^{-1}$	$202.5 \pm 6.0^* (32.4 \pm 0.96^\dagger)$	196.2 ± 3.9	0.0 ± 0.0
Egg proteins, $\text{mg} \cdot \text{kg}^{-1}$	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Peanut proteins, $\text{mg} \cdot \text{kg}^{-1}$	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

Values are means $\pm$ SD of duplicate determinations.

* Converted to milligrams per kilogram of dry powder.

† Actual measurement of concentration of β -lactoglobulin in liquid (in $\text{mg} \cdot \text{L}^{-1}$)

sure has been put on the United States¹¹ and European Union¹² to legislate accurate and comprehensive food labeling. The European Union regulation on labeling only applies to allergenic ingredients that have intentionally been introduced in a food and does not apply to the presence of allergens in foods that have been introduced unintentionally through the use of common processing equipment or production lines that are in close proximity.¹³ With respect to cross-contamination, the US Food Allergen and Consumer Protection Act calls on the federal government to report to Congress on the number of allergen inspections done of food-manufacturing facilities over a 2-year period and the ways in which these facilities can reduce or eliminate cross-contact and to consider revisions of the US Food Code to provide allergen-free preparation guidelines for restaurants and food-service establishment.

This case report emphasizes that additional attention must be given to the prevention of cross-contamination of foods by ensuring quality control of food-preparation practices.

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Shellenbarger S. *Wall Street Journal.* August 18, 2005

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