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CASE REPORT

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Drug or food anaphylaxis?

Catalina Gomez-Galán[a,b]*, Bélgica Minaya-Polanco[b], Martha Jiménez-Freites[b], Julián Andrés Manrique Niño[b], Adrianna Machinena-Spera[b]

[a]*Allergy Unit, Consorci Sanitari Alt Penedès-Garraf, Barcelona, Spain*
[b]*Pediatric Department, pediatric allergy out-clinics, Consorci Sanitari Alt Penedès-Garraf, Barcelona, Spain*

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Abstract
A 9-month-old infant with a personal history of atopic dermatitis and no family history of atopy presented to the outpatient allergy clinic for evaluation of suspected food and drug allergy. The mother breastfed the infant from birth and had introduced only fruits and vegetables into his diet. After the first dose of Ferplex® (iron protein succinylate), the infant had an immediate moderate systemic reaction that required emergency care and treatment with intramuscular epinephrine. The drug was indicated for the treatment of acute anemia. Skin prick test and specific IgE were done, confirming sensitization to cow's milk and egg proteins. It was determined that the baby was sensitized to cow's milk proteins, without prior ingestion, and experienced an anaphylactic reaction after taking Ferplex®, a pharmaceutical product that contains casein as part of its active ingredients. The presence of succinylated casein was confirmed, without pertinent information on the amount in the technical sheet or package insert. Existing pharmaceutical industry regulations should be modified in order to declare food allergens present in excipients and in active ingredients to avoid potential risks for allergic patients. A detailed food history is important in young children who are gradually being introduced to new foods, and in those that have not yet been introduced, recordings should be made to avoid this type of allergic reaction.

***Corresponding author**: Catalina Gómez Galán, Allergist, Allergy Unit, Consorci Sanitari Alt Penedès-Garraf, Barcelona, Spain. *Email address*: cgomezg@csapg.cat

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Introduction

Cases of food allergies are becoming more and more common in pediatric allergy outpatient clinics. Foods involved vary according to age, with allergies to cow's milk and egg being the most frequent in children under 2 years of age.[1] Regarding regulation of food allergens in the industry, there is a difference depending on whether it is food or pharmaceutical industry. Actually, RIAC 1169/2011 (Regulation on food information provided to consumers) requires the mandatory declaration of the presence of 14 food allergens at the European level[2] (Table 1). Pharmaceutical industry regulations do not clearly stipulate how information should appear in relation to the presence of food allergens. The current legislation stipulates that only 5 of the 14 food allergens must be declared in the food industry, one of which is lactose found in cow's milk, while the declaration of cow's milk proteins is not required[3,4] (Table 1).

Iron protein succinylate is a supplement composed of iron bound to succinylated milk proteins (caseins), which enables a ferroprotein complex to increase digestive tolerance, improving taste and increasing iron absorption. These complexes are available in Spain since 1993 and are indicated in the treatment of iron-related ailments in children and adults. The use of iron protein succinylate is contraindicated in patients allergic to cow's milk. There is no specific mention of proteins on the packets of cow milk. At the end of the leaflet in the additional information, there is a mere mention of proteins without any indication of casein.[5,6]

Drugs in which the allergen is part of the active ingredient and the difficulty of locating information is likely to cause problems are those that contain lysozyme, ovalbumin, ovomucoid, and casein. Lysozyme is a protein that can be obtained from egg white or by biofermentation, so it is essential to know its origin; ovalbumin, the main protein in egg white, along with ovomucoid, is considered as one of the most relevant allergens in eggs, and iron protein succinylate that contains casein is the most relevant allergen in cow's milk.[5,7]

Table 1 Notifiable allergens in foods and notifiable excipients in medicines.

Allergens	Foods	Excipients
Cereals with gluten	Yes	Yes
Crustaceans	Yes	No
Eggs and derivatives	Yes	No
Fish and derivatives	Yes	No
Peanuts	Yes	Yes
Soybeans	Yes	Yes
Milk and derivatives	Yes	Lactose
Nuts	Yes	No
Celery and derivatives	Yes	No
Mustard and derivatives	Yes	No
Sulfur dioxide and sulfites	Yes	Yes
Lupins and derivatives	Yes	No
Molluscs and derivatives	Yes	No

Case Report

A 9-month-old boy with no family history of atopy presented with moderate atopic dermatitis. He was referred to the pediatric allergy outpatient clinic for a suspected food allergy. The pediatric report indicated a history of a generalized urticarial reaction after the ingestion of an egg omelette at 6 months and similar symptoms after the ingestion of a kiwi at 8 months. In the week prior to the first visit, the patient had a moderate systemic reaction with generalized urticaria, labial angioedema, and vomiting, which required a visit to the emergency room and treatment with intramuscular adrenaline. The family denied ingesting any foods suspected of causing an allergy (eggs or kiwi). During the interview, the family members recalled that 1 hour before the onset of symptoms, he had been given the first dose of Ferplex® as a treatment for iron deficiency anemia. Ferplex® is a drug that contains iron protein succinylate, blackberry flavor, E-420, propylene glycol, E-217, sodium saccharin, sodium hydroxide, and purified water.[6] This was the first time the patient had taken this medication. A more detailed anamnesis was carried out. The mother reported that he was exclusively breastfed until 6 months of age, and that she continues to breastfeed him without introducing cow's milk into his diet.

Allergological studies were performed. Skin prick tests were performed with commercial extracts (cow´s milk (Roxall®), α-lactoalbumin (Roxall®), β-lactoglobulin (Roxall®), casein (Diater®)). Blood tests show: total IgE 256 KU/L, normal basal tryptase levels (5 mcg/L), and specific IgE levels (ImmunoCAP-Phadia) to cow's milk and egg proteins (Table 2). The quality department of the laboratory manufacturing Ferplex® was consulted to determine the concentration of cow's milk protein present in the drug, and the case was reported to the Pharmacovigilance Service of the same laboratory, who subsequently reported the reaction to the Spanish Agency of Medicines and Medical Products (SAMMP).

Discussion

The conjugation of iron with proteins is a strategy to increase the absorption and digestive tolerance, improving

Table 2 Prick test results and food-specific IgE levels.

Food	Prick test in mm	Specific IgE in KU/L
Cow´s milk	10 × 7	80
Lactoalbumin	10 × 10	49.70
Lactoglobulin	10 × 5	30
Casein	6 × 6	50
Egg white	7 × 7	25
Yolk	5 × 5	2
Ovalbumin	6 × 7	15
Ovomucoid	6 × 6	20
Kiwi	Negative	<0.1
Histamine	5 × 5	
Physiological serum	Negative	

the taste of iron, thereby increasing the compliance and efficacy of anemia treatment in children. Ferplex® was introduced in the Spanish market in 1993 as an iron protein succinylate. There is no reference to its casein content in the technical data sheet.[7,8] The product is a significant source of casein, the original raw material, and iron protein. Before being mixed with the excipients in the drug, it contains 72% milk protein (casein), according to the quality department of the manufacturing laboratory. It is estimated that this percentage decreases with the manufacturing process because of temperature changes, but the laboratory confirms that the percentage of the final product is still high. In 2006, Larramendi et al. published the case of a 4-year-old atopic child with cow´s milk allergy, who developed a mild systemic allergic reaction after the first dose of Ferplex®.[8] This child was diagnosed with cow's milk allergy at 5 months of age. At 2 years, the diagnosis was confirmed by skin tests, IgE determination, and exposure to 5 mL of milk. The reaction that occurred with the iron preparation was more serious than the previous reactions (at onset and at oral food challenge), with angioedema, dyspnea, rhinitis, and perioral erythema. The allergenicity of the Ferplex® product is showed by positive skin tests and IgE, and also the ability to produce an allergic reaction in vivo and in vitro (EAST). Moreover, in three other patients with cow's milk allergy, allergenicity was demonstrated, although they were not exposed to the iron preparation.[8] The amount of modified casein used was 575 mg for every 15 mL of Ferplex®, equivalent to the amount of casein present in cow's milk.[7,8]

After reviewing the literature, we did not find a case similar to ours; this is the first case in which a 9-month-old infant, sensitized to cow´s milk proteins without prior ingestion, developed anaphylaxis after taking a drug containing casein among its ingredients.

In 2010, the Drug Allergy Committee of the Spanish Society of Allergology and Clinical Immunology (SEAIC), in collaboration with the Spanish Agency for Medicines and Health Products (AEMPS), created a document to identify those drugs that could be dangerous when administered to patients with food allergies. These drugs included those that contain derivatives of crustaceans, cow's milk, eggs, fish, soy lecithin, fruit flavors, or essences and probiotics. The document provides a review of the available studies and the adequacy of the information in the technical sheets and prospectuses at that time.[7]

In Spain, there is a national database of adverse drug reactions, the Spanish Pharmacovigilance and Adverse Reaction Database (SPARD), where several cases of reactions with iron protein succinylate have been reported as "allergic diseases" in individuals with a known history of allergy to cow's milk.

We must bear in mind that one of the quality guarantees included in the legislation is that "every drug must have its qualitative and quantitative composition perfectly established." However, as there are no specific regulations, some drugs that contain food allergens among the active ingredients remain unknown. It is hoped that in future reviews of the technical sheets and prospectuses, this information will be improved upon.

Allergy to cow's milk proteins is the most common food allergy in early childhood, followed by egg allergy.[1] Having an allergy to one food predisposes to having other food allergies. Children under the age of 1 year generally present with cow´s milk allergy, and the study of this allergy should also rule out a possible sensitization to egg. This is usually the most frequent scenario in pediatric allergy outpatient clinics. However, this was not the case with our patient, who initially experienced symptoms of egg allergy.[1] After the appearance of allergic reactions to any food, obtaining a detailed food history is very important, in order to know which foods are tolerated and which ones have not yet been introduced. In the case report, our patient had a previous sensitization to cow's milk proteins through breastfeeding.

Therefore, in the case of patients with a food allergy, especially children, it is necessary to consider the possibility that prescribed medications could contain food allergens.

Conclusion

In all patients with food allergies, hidden sources of allergens present in medications should always be considered. Once a food allergy has been diagnosed, a detailed review of food tolerance and regular food intake should be checked. It is of special interest to report suspected adverse reactions to drugs in which food allergens are present and to clearly state this situation in the medical history. It is important to improve regulation regarding the presence of food proteins in excipients and active ingredients by the pharmaceutical industry and thereby minimize the risk of reactions.

Authors Contributions

All authors contributed equally.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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