

Potential Hypersensitivity due to the Food or Food Additive Content of Medicinal Products in Spain

Document Written by the Drug Allergy Committee of the Spanish Society of Allergology and Clinical Immunology (Sociedad Española de Alergología e Inmunología Clínica, SEAIC)

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■ Abstract

The Drug Allergy Committee of the Spanish Society of Allergology and Clinical Immunology reviewed the allergenic potential of several substances of food origin that are found in the composition of some drugs. Despite recent legislation on labeling, many labels do not clearly state whether the drug contains raw material (active ingredients, excipient, or other manufacturing intermediate) with an origin in any of the substances in the list of the 14 groups of food allergens that are subject to mandatory declaration. The objective of legislation is that the drug package, the Summary of Product Characteristics, and the patient information leaflet clearly state the food content in order to improve the safety of allergic patients.

Therefore, any food or allergen derivative that must be declared should be clearly stated on the drug label. Of all the evaluated products, egg and milk derivatives are the most frequently discussed in literature reviews. The natural or synthetic origin of potentially allergenic substances such as lysozyme, casein, lactose, albumin, phosphatide, and aromatic essences should be clearly stated.

Providing this information has 2 clear advantages. First, allergic reactions to drugs in patients with food allergy could be avoided (if the substances have a natural origin). Second, prescription would improve by not restricting drugs containing synthetic substances (which do not usually induce allergic reactions).

Key words: Food allergy. Drug allergy. Additive. Egg. Milk.

■ Resumen

El comité de alergia a medicamentos ha revisado el potencial alergénico de diversas sustancias de origen alimentario que pueden formar parte de algunos medicamentos. Aunque la nueva normativa de etiquetado de alimentos se ha desarrollado recientemente, en el etiquetado de muchos medicamentos no figura de forma clara si contienen en su composición materias primas (tanto principios activos, como excipientes u otros intermedios de fabricación) cuyo origen esté en alguna de las sustancias de la lista de los 14 grupos de alérgenos de declaración obligatoria en los alimentos. El objetivo final es que tanto en el etiquetado del envase, como en la ficha técnica y el prospecto de los medicamentos figure de forma clara su contenido en alimentos para mejorar la seguridad de los pacientes alérgicos.

Como conclusiones podemos afirmar que en general es deseable que cualquier producto derivado de alimentos y alérgenos de declaración obligatoria figure con letra clara en los etiquetados de los medicamentos. Dentro de todos los productos evaluados podemos concluir que los derivados del huevo y la leche son los que más se han recogido en las revisiones bibliográficas realizadas. Debería figurar tanto en el prospecto como en la ficha técnica de los medicamentos el origen natural o sintético de sustancias como: lisozima, caseína, lactosa, albúminas, fosfátidos y aromas entre otras potencialmente alergénicas.

Completando esta información podríamos obtener dos ventajas claras:

1. Se evitarían reacciones alérgicas a medicamentos en pacientes con alergia alimentaria (si las sustancias son de origen natural)
2. Se mejoraría la prescripción por parte de los facultativos no restringiendo aquellos fármacos que contienen sustancias de origen sintético (que no suelen inducir reacciones alérgicas).

Palabras clave: Alergia alimentaria. Alergia a medicamentos. Conservantes. Huevo. Leche.

Introduction

According to Spanish legislation [1,2] on the guarantees and rational use of medicinal products and devices, which governs areas such as drug labeling, all excipients that have to be declared must be clearly stated on the label. These excipients are regularly updated by the European Union [1-3]. Both the labeling and the patient information leaflet must be consistent with the Summary of Product Characteristics (SPC) and should include the necessary information for the medicinal product to be correctly administered. In the case of topical, injectable, or ocular preparations, the labeling should specify all the excipients, not just those that are required to be declared by law [1].

An excipient is any component of the medicinal product other than the active substance [4]. However, this definition does not include impurities or residues of substances used in the manufacturing process. Noninclusion of residues and impurities and the list issued by the European Community clearly contradict current Spanish regulations on food allergies (Royal Decree 1245/2008), according to which a series of 14 allergens must be declared when they are present in the composition of foods or when traces of such allergens are found in food products. The 14 allergens are cereals containing gluten, crustaceans, eggs, fish, peanuts, soybeans, milk, nuts, celery, mustard, sesame seeds, sulfites, lupines, and mollusks) [5]. The list was drawn up in response to a report by the European Food Safety Authority based on the European Directive that governs the labeling, presentation, and advertising of foodstuffs.

Furthermore, any medicinal product containing excipients with a recognized action or effect should be declared in full, and a warning statement is considered necessary [1]. Therefore, given the recognized allergenic potential of small amounts of food proteins in patients who can develop severe reactions to them, it would appear logical to consider the foods contained in some medicinal products—either as the active substance or as excipients—as hidden allergens.

This article is the result of a review that was conducted by the Drug Allergy Committee of the Spanish Society of Allergology and Clinical Immunology (SEAIC) to confirm or rule out the significance of food additives contained in medicinal products. Its objective is to identify medicinal products that are potentially dangerous for allergic individuals, as well as products that pose no risk and therefore need not be avoided.

Glucosamine and Other Chitin Derivatives Found in Crustaceans

Glucosamine is a natural substance that is found in the body and is involved in proteoglycan synthesis. Proteoglycans, which are formed by sugars and proteins, are found in cartilage and can be used for the treatment of arthritis and osteoarthritis, as well as for cartilage reconstruction.

Glucosamine is an amino sugar found mainly in fungi and in the exoskeleton of crustaceans and arthropods. The chitin in crustaceans is a source of several pharmaceutical preparations: glucosamine (obtained by total depolymerization), chitosan derivatives (obtained by deacetylation), and chito-oligomers (obtained by partial depolymerization). Glucosamine is synthesized commercially by hydrolysis of crustacean exoskeletons. Recent studies have shown that the procedures used to isolate chitin derivatives from shellfish also remove proteins, fats, and other contaminants. This means that this substance does not contain clinically relevant traces of crustacean allergen. Therefore, it does not pose a risk for patients with shellfish allergies [6].

Native chitin found in biological structures (covalently bound to proteins in arthropods and covalently bound to glucans in fungi) is able to induce allergic responses and should not be confused with the industrially processed purified substance, which does not pose a health risk for allergic patients [6].

In 2004, Gray et al [7] recruited 6 patients diagnosed with systemic allergy to shellfish and found that they simultaneously presented negative skin test results to glucosamine and positive skin test results to shellfish. The patients then underwent an oral challenge test and tolerated 500 mg of glucosamine.

In 2006, 15 patients who met the criteria for shrimp allergy underwent oral challenge tests with 1500 mg of shrimp-derived glucosamine and of synthetic glucosamine. Good tolerance to both products was observed [8].

Conclusions

At present, the Spanish Agency for Medicines and Health Care Products (AEMPS) lists 48 pharmaceutical presentations in Spain that have glucosamine sulfate as their active substance. This list includes Xicil, Hespercorbin, Cartisorb, Coderol, Active Complex, and Articuflex.

In the light of the articles reviewed, the SEAIC Drug Allergy Committee believes that patients with shellfish allergy are not currently at risk of suffering allergic reactions if they take chitin derivatives, including glucosamine. This statement also applies to patients who are allergic to arthropods (including mites), fungi, and/or parasites. Therefore, it is not necessary to add specific warnings in the SPC for individuals with these allergies.

Lysozyme

Lysozyme (acetyl muramidase) is an enzyme with bactericidal activity and a molecular weight of 14.3 kDa. It is obtained from egg white or through biofermentation. The United States Food and Drug Administration (FDA) does not accept it as a medicinal product. Lysozyme is used in empirical treatment. Eggs contain 3% lysozyme, which has been characterized as an allergen (Gal d 4). Up to 32% of individuals with egg allergy are sensitized to lysozyme [9].

Most lysozyme (E1105) used in food products is not derived from eggs, but is obtained by biofermentation. When lysozyme is obtained from eggs, this should be stated on the label.

The AEMPS lists 7 lysozyme-containing drugs that are on the Spanish market. The national code has been revoked in the case of 3 of these drugs; therefore, they are no longer marketed (Table 1). The list of marketed products is as follows:

- Lisozima Chiesi 250-mg tablets (with prescription)
- RinoDexa nasal drops in solution (with prescription)
- Trofalgon capsules (over the counter)

Other marketed lysozyme-containing drugs are used to treat respiratory tract infections (Anticatarral Alesa, Bucometasona, Disneumon Pernasal, Espectral, Lisokana, Normonar, Poliririno, Pulmitropic) and as tonics and supplements (Creci Baby Drops). These products do not specify the lysozyme source.

Allergic Reactions

The lysozyme present in some drugs has caused allergic reactions [10,11] that have manifested as angioedema [12], urticaria, and even anaphylaxis [13]. There is one case report of toxic epidermal necrolysis [14] and another of an infant in whom sensitization occurred through maternal use of ointment to treat a cracked nipple [15].

Some of these patients were previously sensitized to egg, while in others lysozyme was the primary allergen. Lysozyme has also been implicated as an occupational asthma-inducing allergen in workers in the pharmaceutical industry [16] and in bakers [17].

Conclusions

At present, lysozyme is the active ingredient in 4 medicinal products, none of which state its source.

The manufacturers should be requested to state in both the patient information leaflet and the SPC whether the lysozyme used in their products was obtained from eggs. In this case, the products should include a specific contraindication to their use in patients with egg protein allergy.

The SEAIC Food Allergy Committee issued a statement to the effect that it would be appropriate to make recommendations for individuals with egg allergy to systematically avoid medicinal products containing lysozyme and ovalbumin.

Table 1. Data Provided by the Manufacturer for Drugs Containing Lysozyme Marketed in Spain

Product	Quantity of Lysozyme	Egg as Source	Are Contraindications Stated in Case of Egg Allergy?
Lisozima Chiesi	250 mg	NS	No SPC, no patient information leaflet
Lizipaina	5 mg	NS	Allergy to any component
Rino Dexa ped (nose drops)	1 mg/10 mL	NS	Not specified
Trofalgon capsules	40 mg	NS	No SPC

Abbreviations: NS, not stated; SPC, Summary of Product Characteristics.

Iron Protein Succinylate With Cow's Milk Protein

Preparations containing iron protein succinylate bind the iron to succinylated casein to improve digestive tolerance and flavor and to increase iron absorption. These preparations were marketed for the first time in Italy in 1986 and have been available in Spain since 1993 for treatment of anemia in both pediatric and adult patients. They are currently marketed in Europe, South America, and, since 2003, the United States. Specifically, Ferplex is a significant source of casein, because it contains a similar proportion to the casein found in cow's milk (each 15 mL vial contains 575 mg of modified casein).

The AEMPS reports that some drugs on the Spanish market (Table 2) contain casein in the form of iron protein succinylate in drinkable vials. These drugs include Ferplex, Ferrocur 800 mg, and Lactoferrin 800 mg.

Allergic Reactions

A well-documented systemic reaction following the intake of a single drinkable vial of Ferplex 40 was reported in a 4½-year-old child diagnosed with cow's milk oral allergy syndrome at 5 months of age [18]. When the child was 2 years old, the diagnosis was confirmed by skin tests, determination of immunoglobulin (Ig) E, and oral challenge with 5 mL of milk. The reaction to the iron preparation was more severe than the previous reactions (both the spontaneous and oral challenge-induced reactions), progressing with angioedema, dyspnea, rhinitis, and perioral erythema. The authors demonstrated the allergenicity of Ferplex (skin tests and IgE), as well as its ability to cause an allergic reaction, using both *in vivo* and *in vitro* techniques (enzyme allergosorbent test) in the patient

and in 3 individuals with casein allergy who did not undergo the iron preparation challenge.

Other than this case report, we were unable to find any other references to allergic reactions.

Conclusions

The SEAIC Drug Allergy Committee believes that pharmaceutical companies should state in both the patient information leaflet and the SPC that the product contains cow's milk-derived casein in the active substance. At present, this is only stated in the contraindications and pharmacological properties. In the case of iron protein succinylate, the equivalent content of casein should be stated—this is quantitatively high and potentially dangerous—as should its milk origin.

Ovalbumin

Ovalbumin (Gal d 2), the main protein in egg white, is considered to be one of the most significant egg allergens, together with ovomucoid. This glycoprotein belongs to the serpin superfamily, as do antithrombin and antitrypsin. The biological function of ovalbumin is not clear, although it is thought to be a storage protein for reproduction in hens and could also play a protective role against exogenous bacteria attacking the egg. In hen egg, ovalbumin is made up of about 385 amino acids, and its relative molecular weight is 45 kDa. It was artificially synthesized in 1980, and its content in food is subject to regulation by health authorities.

The AEMPS reports that certain drugs on the Spanish market contain ovalbumin in the form of ferrimannitol-ovalbumin (Table 3). These drugs include the following:

Table 2. Data Provided by the Manufacturer for Drugs Containing Iron Protein Succinylate With Cow Milk Protein Marketed in Spain

Product	Quantity of Iron Protein Succinylate	Milk as Source	Are Contraindications Stated in Case of Milk Protein Allergy?
Ferplex	40 mg/15 mL (ampoules)	Yes	Yes
Ferrocur	40 mg/15 mL (ampoules)	Yes	Yes
Lactoferrin	40 mg/15 mL (ampoules)	Yes	Yes

Table 3. Data Provided by the Manufacturer for Drugs Containing Ovalbumin Marketed in Spain

Product	Quantity of Ferrimannitol-Ovalbumin ^a	Egg as Source	Are Contraindications Stated in Case of Egg Allergy?
Ferroprotina	100 mg/10 mL (ampoules) 100 mg (sachets)	NS	Yes
Kilor	300 mg (sachets)	NS	Yes
Profer	300 mg (sachets)	NS	Yes

- Ferroprotina: 20 mg in oral solution (ampoules) and 40 mg in granulate for oral solution
- Kilor: 300 mg granulate in sachets
- Profer: 300 mg and 600 mg granulate in sachets

Furthermore, antiviral vaccines containing ovalbumin include the following:

- Influenza-virus vaccines: Evagrip, Imuvac, Inflexal Berna, Mutagrip, Antigripal Poli Leti, Antigripal Pasteur, and Fluairix
- Yellow fever vaccine: Stamaril
- Measles vaccine: Antisarampión Llorente
- Mumps vaccine: Antiparotiditis MSD
- MMR (measles, mumps and rubella): MSD triple

No other products on the market contain ovalbumin. However, ovalbumin is used in its pure form (coated tablets) as a protein supplement in sports diets, especially in strength sports such as bodybuilding (Supergigante, Lab SND, Argentina).

Allergic Reactions

No allergic reactions to ferrimannitol-ovalbumin have been reported in the medical literature [19,20]. Isolated cases of allergy to oral iron in the form of ferrous sulfate have been reported [21].

Viral vaccines grown in chick embryo may contain egg protein traces. These vaccines include MMR vaccine, influenza virus vaccine, yellow fever vaccine, and some hepatitis A presentations (Epaxal). However, prospective studies have demonstrated the safety of MMR vaccine in children with egg allergy (the vaccine contains only a few picograms of ovalbumin) [22]. Therefore, international pediatric consensus statements no longer recommend allergy studies before administration of this vaccine in children with egg allergy. Caution is only advised in cases of anaphylaxis: the vaccines should be administered in a center that is equipped to treat a possible reaction [23,24].

With the exception of the MMR vaccine, the presence of ovalbumin (measured in micrograms in today's vaccines) is still a formal contraindication for prescribing vaccines propagated in chick embryos to patients with allergy to egg, chicken, or both. Examples of such vaccines are purified rabies vaccine (grown in chick embryo fibroblasts), influenza virus vaccine (grown in the allantoic fluid surrounding the chick embryo), and yellow fever vaccine (grown in chick embryos). In view of the above remarks and the weaker immunizing power of alternative preparations, the current recommendation is to administer the MMR vaccine in a hospital setting [25]. In the case of the influenza virus and yellow fever vaccines, skin tests should be performed beforehand, batches containing <1.2 µg of ovalbumin/mL should be selected, and a gradual 2-dose administration regimen should be used [22,25].

Conclusions

Ovalbumin is not found as the active substance in any currently marketed drug. There have been no reports of ferrimannitol-ovalbumin allergy.

Pharmaceutical companies should state in both the patient information leaflet and the SPC whether the ovalbumin has

been obtained from eggs. If this is the case, the product should include a warning against use in patients with egg protein allergy. In the case of ferrimannitol-ovalbumin, the equivalent content of ovalbumin should be stated, as should its origin.

The SEAC Food Allergy Committee statement states that it would be appropriate to make recommendations for individuals with egg allergies to systematically avoid medicinal products containing lysozyme and ovalbumin [22]. Furthermore, before taking any new medicinal product, allergic individuals should ensure—checking with their doctor if necessary—that the product does not contain egg proteins. Patients are advised to warn doctors and pharmacists that they suffer from egg allergy.

Lactose

Lactose (β -D-galactopyranosyl-D-glucopyranose) is a carbohydrate disaccharide formed by a glucose molecule binding to a galactose. It is found only in milk. More specifically, it involves a β -galactopyranose and a β -glucopyranose bound by carbons 1 and 4, respectively. When the 2 monosaccharides bind together, a water molecule is produced. Furthermore, this compound contains a hemiacetal hydroxyl, thus inducing the Benedict reaction.

Lactose crystallizes with a water of hydration molecule ($C_{12}H_{22}O_{11} \cdot H_2O$), also known as lactose monohydrate. The molar mass of lactose monohydrate is 360.32 g/mol; that of anhydrous lactose is 342.30 g/mol.

When lactose is used as an excipient, it enhances the stability, efficacy, and safety of the active substance in the medicinal product. It is used in tablets to enhance their solubility and flavor, although it can also be found in other presentations (vials, suspensions, inhalers). In the pharmaceutical industry, it forms the base of more than 20% of prescription drugs and approximately 65% of over the counter medicinal products. Currently, 808 drugs contain lactose as an excipient [26]. Lactose must be declared on the label.

Allergic Reactions

Some authors have reported allergic reactions to drugs containing lactose in patients with cow's milk protein (CMP) allergy [27-30], where the lactose contained CMP as a result of a defective purification process. It could well be essential to know which method was used to obtain the lactose, because CMP contamination can only occur when the lactose is of animal origin, not if it is synthetic. Other authors [31], however, found no relationship between lactose and CMP allergy.

Conclusions

While it is true that a large number of drugs contain lactose as an excipient, there are few reports of allergic reactions to these drugs in patients with CMP allergy. We recommend that patients with severe CMP allergy should be treated with drugs—especially when administered intravenously—whose labels state that the lactose contained in the preparation is not of animal origin. In any event, depending on the need for treatment, the patient should be referred to the allergy

department in order to rule out sensitization to the drug in question.

Pharmaceutical companies should state in both the patient information leaflet and the SPC whether the lactose is of natural or synthetic origin. This would completely eliminate the risk in patients who are sensitive to trace amounts.

Probiotics

Probiotics are live microorganisms that are added to food. They remain active in the intestine and cause significant physiological effects. Probiotics help to balance host intestinal bacteria and boost the immune system. They can travel through the gastrointestinal tract and may be recovered alive in feces, although they also adhere to the intestinal mucosa.

There are several pharmaceutical presentations of probiotic food products in the form of sachets or capsules (Casenfilus sachets, Infloran capsules, Lacteol capsules and sachets, Lactofilus powder)

Only a few species of lactic bacteria can be classified as probiotics, mainly because the live microorganism count must remain sufficiently high to overcome the obstacles encountered in the digestive tract. These species include entities such as *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Bifidobacterium bifidus*, and *Bifidobacterium longum*.

Allergic Reactions

There are no reports of allergic reactions to probiotics as components or excipients in any medicinal products.

Conclusions

The SEAIC Drug Allergy Committee believes that there is no risk of allergic reactions to drugs containing probiotics.

Soybean Lecithin

Isoflavones are a subclass of vegetal flavonoids that have a similar chemical structure to that of estradiol. The 3 main free forms of isoflavones are genistein, daidzein, and glycitein, and the 2 minor forms are formononetin and biochanin A. Isoflavones are mainly absorbed as aglycones.

Allergic Reactions

According to various studies, intake of isoflavones in the form of soybean products is safe. However, with regard to soybean-based formulations for children, insufficient experimental data in humans and animals means that it is impossible to determine isoflavone toxicity [32].

Isoflavones are included as excipients in certain medicinal products and/or in lipid emulsions used for parenteral nutrition. Although adverse reactions have been reported due to inhalation of bronchodilators with soybean lecithin as an excipient, the causal relationship is doubtful. A child with peanut allergy suffered an asthma exacerbation and generalized urticaria 1 hour

after the second inhalation of ipratropium bromide (Atrovent), which contains soybean lecithin in its excipients [33]. A woman suffered paradoxical bronchospasm with laryngospasm after using different inhalers containing soybean lecithin as an excipient, although she was not allergic to soybean [34]. There are also case reports of allergic reactions following the administration of parenteral nutrition formulations based on soybean oil (Lipofundin) [35,36]. However, in one case, a fish oil formulation that also contained soybean oil was used as an alternative and was well tolerated by the patient [37].

Occupational asthma has been reported in the food industry [38]. Some hydrolyzed milk formulas contain soybean lecithin [39]. The presence of soybean protein in oil, lecithin, and margarine has also been reported [40]. The allergenicity of these residual proteins has been demonstrated using the radioallergosorbent test [41].

Medicinal products found to contain soybean lecithin or soybean include Atrovent, Combivent, Rapamune tablets (soy fatty acids), fish oils (soybean oil), Rythmol SR (soy lecithin), Alinia (soy lecithin), Caprylidene, Diprivan (soybean oil), and propofol (soybean oil).

Conclusions

The presence of soybean protein has been demonstrated in soybean lecithin. Medicinal products containing lecithin as an excipient should not be administered to patients with soybean allergy; in cases of doubt, tolerance should be determined by means of challenge tests.

Fish Oil

Fish oil-based supplements (eg, intravenous SMOFLipid [with soybean oil, olive oil, and fish oil rich in ω -3]) can be used for parenteral nutrition. However, we found no case reports of fish-allergic patients who had an allergic reaction following the administration of these formulations. One study of 6 patients with fish allergy demonstrated that these supplements were well tolerated [42].

Conclusions

There have been no case reports of allergic reactions to medicinal products containing fish oil.

The SEAIC Drug Allergy Committee therefore considers that there is no risk for patients with fish allergy.

Egg Phosphatide and Egg Lecithin

Egg lecithin is a glycerophosphate or glycerophospholipid with the structure of phosphatidylcholine. All marketed egg phosphatides are extracted from egg yolk. Soybean is another significant source of phosphatide. The food additive E322 is lecithin, regardless of its origin.

In view of their emulsifying action, egg phosphatide and egg lecithin are included as excipients in certain drugs. They are also components of some lipid emulsions used in parenteral

nutrition, since they are a source of essential fatty acids. Although these excipients and products are highly purified, hypothetically, they could contain residual proteins that cause allergic reactions in patients with egg allergy. In addition, despite the presence of proteins in drug formulations containing egg phosphatide and egg lecithin [43], the list of excipients subject to mandatory declaration does not include them.

At present, the only drugs that include egg phosphatide and lecithin in their excipients or composition are propofol and lipid emulsions for parenteral nutrition.

• Propofol

Propofol (2,6-diisopropylphenol) is a short-acting intravenous drug with potent sedative and hypnotic properties. It is routinely used for the induction of general anesthesia in adults and children over the age of 3, for maintenance of anesthesia in adults and children over the age of 2 months, for sedation in patients requiring ventilation in intensive care units, and for light sedation in surgical procedures and diagnostic techniques such as endoscopy. Propofol is poorly soluble in water and is therefore marketed as an emulsion. Current formulations contain 1% or 2% propofol (wt/vol) and the vehicle contains 1.2% egg phosphatide/highly purified egg lecithin, 10% soybean lecithin, 2.25% glycerol, sodium hydroxide, and water. It also incorporates metabisulfite or EDTA to inhibit bacterial and fungal growth [44] (Table 4).

Most hypersensitivity reactions to the different formulations of propofol have been attributed to propofol itself, and some publications have demonstrated the existence of specific IgE to this active substance [45].

However, bronchospasm associated with the metabisulfite content of the propofol vehicle has been reported [46], as have hypersensitivity reactions in patients who are allergic to legumes (attributed to the presence of soybean lecithin in the vehicle), in patients allergic to eggs and soybean, and in patients allergic to egg.

There have been 2 isolated case reports of anaphylactic reactions in patients with egg allergy, and both were attributed to the presence of egg phosphatide/egg lecithin in propofol formulations. In 1994, Bassett et al [47] published a case of generalized pruritus following administration of propofol (Diprivan) in an adult patient with egg allergy and no history of allergy to other foods or drugs (eg, antibiotics or anesthetic agents). The causal relationship between egg hypersensitivity and the drug-induced reaction was not confirmed by an allergy study. In 2003, Hofer et al [48] reported the case of a 14-month-old child who experienced hypotension, tachycardia, and bronchospasm following administration of propofol and rocuronium before intubation. The patient was allergic to eggs, peanut oil, and fungi. The child did not undergo an allergy study, and tolerance to rocuronium was not tested afterwards. The authors diagnosed anaphylaxis and suggested that egg allergy was the possible cause of the reaction to propofol.

Only 1 allergy study has investigated sensitization to the propofol vehicle. In 1998, Lizaso Bacaico et al [43] used skin tests to analyze sensitization to propofol (Diprivan) and its vehicle (Intralipid: 1.2% egg phosphatide/highly purified egg lecithin, 10% soybean lecithin, 2.25% glycerol) in a study of 25 patients allergic to egg, legume, or both who underwent skin tests with whole egg, white and yolk, soybean lecithin, legumes, Diprivan, and Intralipid. All patients had negative

Table 4. Propofol Formulations Marketed in Spain

Name of the Medicinal Product	Marketing Authorization Holder	Excipient
Diprivan 1%, ampoule Diprivan 1%, prefilled syringe Diprivan 2%, prefilled syringe Diprivan 2%, vial Diprivan 1%, vial	Astrazeneca Farmaceutica. Spain, S.A	Soybean oil and purified egg phosphatide
Propofol Fresenius 10 mg/mL, emulsion for injection or infusion Propofol Fresenius 20 mg/mL, emulsion for injection or infusion Propofol Fresenius 10 mg/mL, Fresenius emulsion for injection or infusion Propofol Lipomed 20 mg/mL, Fresenius emulsion for injection or infusion	Fresenius Kabi Deutschland GmbH	Soybean oil and purified egg phosphatide
Propofol-Lipuro 1% Propofol-Lipuro 2% (20 mg/mL), injectable emulsion Propofol-Lipuro 5 mg/mL, emulsion for injection or infusion	B. Braun Melsungen AG	Soybean oil and egg lecithin
Propofol Mayne 10 mg/mL, emulsion for injection and infusion Propofol Mayne 20 mg/mL, emulsion for injection and infusion	Mayne Pharma España, S.L.	Soybean oil and egg lecithin
Recofol 10 mg/mL, emulsion for injection or intravenous infusion Recofol 20 mg/mL, emulsion for intravenous infusion	Quimica Farmaceutica Bayer, S.L.	Soybean oil and egg lecithin

results for Diprivan and Intralipid. The authors confirmed the presence of traces of egg and soy proteins in the Diprivan vehicle, although they did not detect sensitization to either Diprivan or Intralipid. They concluded that the most likely cause of the hypersensitivity reaction to Diprivan was propofol and not its vehicle. However, they suggested that it would be interesting to follow these or other patients with allergy to egg and/or legumes, in case they ever required anesthesia with a propofol formulation.

Alternatives to Propofol: Fospropofol Disodium

As mentioned above, propofol is an emulsion formulation of the active substance 2,6-diisopropylphenol, which is not water-soluble. A prodrug, phosphorylated propofol, is synthesized by adding a phosphate group to the diisopropylphenol molecule. This water-soluble formulation of the active substance does not contain egg phosphatide/egg lecithin or soybean lecithin, thus eliminating the potential risk of hypersensitivity reactions following the administration of propofol in patients with allergy to egg and/or legume [49]. Two phosphorylated propofol prodrugs have been synthesized: propofol phosphate and fospropofol disodium (2,6-diisopropylphenoxymethyl phosphate disodium). The FDA approved the use of fospropofol disodium (Lusedra) in December 2009 [50]. Lusedra contains 3.5% fospropofol in water, 0.25% (wt/vol) monothioglycerol, and 0.12% tromethamine [49]. This drug is not marketed in Spain.

• Lipid Emulsions for Parenteral Nutrition Containing Egg Phosphatide/Egg Lecithin

Lipid emulsions for parenteral nutrition contain vegetable oils (mainly soybean oil), and some have egg phosphatide added as a source of essential fatty acids.

Our literature review revealed 4 isolated cases of hypersensitivity reactions to lipid emulsions used for parenteral nutrition. The responsible allergen was only identified in 2 cases, 1 of which involved egg phosphatide/egg lecithin in the anaphylactic reaction.

Buchman et al [51] reported a case of urticaria associated with the administration of Intralipid in an adult patient with AIDS. Urticaria reoccurred when the drug was readministered 2 days later, but not after another lipid preparation, Liposyn II, which contains soybean oil and sunflower oil but does not contain egg phosphatide/egg lecithin. In this case, skin tests with soybean, Intralipid, and Liposyn were negative, but radioallergosorbent testing revealed sensitization to egg white, egg yolk, and soybean proteins. The hypersensitivity reaction was attributed to the presence of egg proteins that contaminated the egg phospholipids during the manufacturing process. However, the authors did not analyze the protein content in the lipid emulsions, and 6 weeks after the anaphylactic reaction, the patient tolerated readministration of Intralipid.

Conclusions

The involvement of egg phosphatide/egg lecithin in drug hypersensitivity reactions is poorly documented in the literature.

Published data on patients with egg allergy rule out sensitization to drugs containing egg phosphatide/egg lecithin in their excipients, namely, propofol formulations and lipid emulsions for parenteral nutrition.

Formulations of fospropofol (a propofol prodrug) are free of egg phosphatide/egg lecithin and may offer a therapeutic alternative to propofol in selected patients with egg allergy who require anesthesia or sedation. Although not marketed in Spain, these formulations may be encountered as foreign medicinal products.

Egg allergy is not an absolute contraindication for drugs containing egg phosphatide/egg lecithin.

The administration of drugs containing egg phosphatide/egg lecithin in patients with egg allergy involves a potential risk of hypersensitivity reaction. Therefore, such agents should be contraindicated in patients with severe egg allergy if alternative therapies are available.

In the light of current data, the SEAIC Drug Allergy Committee considers that drugs containing egg phosphatide/egg lecithin have no identified risk for patients who are allergic to egg protein. However, patients who have experienced severe anaphylactic reactions to egg protein should be assessed by an allergy specialist before using these medicinal products.

Lactic Acid

Lactic acid or lactate (ionized form) is a chemical compound that plays an important role in various biochemical processes, such as lactic acid fermentation. It is produced from pyruvic acid through the enzyme lactate dehydrogenase in fermentation processes. Lactate is produced constantly during metabolism and especially during exercise. Its levels increase when tissue energy requirements (mainly muscle tissue) exceed the available oxygen supply in blood.

Lactic acid is used as a medicinal product, food preservative, and an ingredient in cosmetics. It is a syrupy, colorless or slightly yellow liquid consisting of a mixture of lactic acid, condensation products (eg, lactoyl lactic acid and other polylactic acids), and water. It is obtained by lactic fermentation of glucose or can be prepared synthetically.

Lactic acid is used as a medicinal product through 2 main routes:

- Intravenously, as a source of bicarbonate to treat metabolic acidosis. It forms part of Ringer's lactate solution, which is used as a plasma expander.
- Topically, to treat warts, often in combination with salicylic acid, and in emollient creams. It is also used to treat severe aphthous stomatitis in immunosuppressed patients. There are many different preparations marketed in the form of creams, ointments, lotions, and shampoos.

It is also often used in compounded prescriptions.

Poly-L-lactic acid is commercially available. This biocompatible, biodegradable, and immunologically inert polymer is used subcutaneously, mainly in cosmetic medicine as filler for facial atrophy. It was approved by the FDA in 2004 as a treatment for lipoatrophy secondary to antiretroviral treatment in HIV-infected patients, and in 2009 it was approved for use in the general population.

Two types of hypersensitivity reactions have been reported, as follows:

- Adverse reactions following administration of poly-L-lactic acid as filler in the treatment of lipoatrophy in HIV-infected patients and in the general population. Although poly-L-lactic acid is a safe product, delayed granulomatous reactions may occur in the infiltration area in both HIV-infected patients and in the general population [52-56].
- A contact hypersensitivity reaction has been reported to lactic acid as a component in a wart remover solution [57].

Conclusions

The SEAIC Drug Allergy Committee considers that the risk of allergic reaction to lactic acid is currently very small and involves delayed-type reaction following topical administration of lactic acid and subcutaneous administration of poly-L-lactic acid. Therefore, these products are not contraindicated in patients with CMP allergy.

Aromas/Fruit Essences

Aromas and flavoring are substances and/or mixtures of natural or synthetic products that are added to certain medicinal products in order to mask or enhance their taste and smell. They increase patients' acceptance of medicinal products, especially in pediatric and geriatric populations.

Although these additives may be natural or synthetic, those that potentially cause allergic reactions are likely to be of natural origin, particularly additives derived from fruit. Examples of flavoring agents that are used to mask the taste of drugs include the following:

- Sweet flavors: vanilla, fruit, grapes, and sweet berries
- Acidic flavors: lemon, lime, orange, cherry, raspberry, and blackberry
- Savory flavors: walnut, butter, and cinnamon
- Bitter flavors: anise, coffee, chocolate, mint, cherry, and orange
- Metallic flavors: mint

Allergic Reactions

Although a very large number of pharmaceutical products contain this type of additive, reactions are very rarely reported. In general, fruit flavoring and essences are often chemically modified, and this, together with the minimal amount of fruit used, makes allergic reactions extremely rare, especially in the pharmaceutical industry.

An extensive search of the online and printed literature revealed very few findings. One case report of an episode of urticaria and angioedema immediately after administration of a preparation of oral penicillin with banana essence demonstrated sensitization to banana and good tolerance to penicillin [58]. In this case, allergens in the banana essence matched the patient's specific IgE. In another published case of bronchospasm related to both vanilla and lactose [59], the mechanism involved was not clear. Most publications report

exacerbation of atopic dermatitis related to different food additives, including aromas and essences [60-64].

Published articles on products used in alternative medicine or in natural creams containing fruit essences and flavors (mango, kiwi) report some adverse reactions. These usually involve contact dermatitis caused by fruit oils prepared with fruit essences of questionable standardization (eg, orange, mint, and lemon oil) [65-67]. Essential oils (thus named because of their aroma) are known contact sensitizers.

Conclusions

The SEAIC Drug Allergy Committee considers that patients with fruit allergy are currently at very low risk of suffering allergic reactions if they take drugs containing natural aromas and flavors.

However, manufacturers should state in both the patient information leaflet and the SPC whether the flavors and aromas are of natural or synthetic origin.

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