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Drug Allergy (C Mayorga, Section Editor)

New Challenges in Drug Allergy: the Resurgence of Excipients

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Abstract

Purpose of Review Allergy to excipients is a cause of multidrug allergy and if it is not taken into account, it can lead to unexpected severe reactions. If an excipient allergy is suspected, an accurate examination followed by algorithms is very important for a correct diagnosis and to give patients detailed information in order to avoid future reactions.
Recent Findings In recent times, due to allergy COVID vaccine reactions, interest in excipients as polyethylene glycol derivatives (PEGs) has increased as a possible cause of drug and vaccine hypersensivity. In addition to PEGs many other excipients as gelatin, alpha-gal, protamine, benzalkonium chloride, and benzyl alcohol have been described as a cause of allergy to drugs and vaccines. For most excipients, the dilutions used for skin testing (ST) are not standardized and proper algorithms to reach a diagnosis are not available.
Summary The purpose of this article is to review the excipients that may produce inmediate hypersensitivity drugs and vaccine reactions and update diagnostic procedures to reach an accurate diagnosis. We highlight the in vivo and in vitro diagnostic tests used in published reports and detail the dilution used for each excipient to perform ST in order to confirm this vital pathology and to prevent new reactions.

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Introduction

The European Medicines Agency (EMA) "Guideline on excipients in the dossier for application for marketing authorization of a medicinal product" [1] and the Current Good Manufacturing Practices [2] define an excipient or inactive ingredient as the constituents of the pharmaceutical form other than the active ingredient. It should be noted that in recent times, due to the SARS-CoV2 pandemic and allergic reactions decribed to the COVID-19 vaccines, interest in excipients has increased as a possible cause of drugs and vaccine hypersensitity [3]. For both drugs and vaccines, these are rare reactions; however, for vaccines, they are the primary cause of immediate hypersensitivity reactions (IHRs) [4••].

We should suspect this problem when a patient reports unrelated multiple drug reactions. In this case, an accurate examination followed by algorithms is very important for correct diagnosis and to give patients detailed information in order to avoid future reactions. However, the diagnostic procedure for allergy to excipients is not properly protocolized. The purpose of this article is to review the excipients that may produce inmediate hypersensitivity drug and vaccine reactions and update diagnostic procedures to asses the involvement of each excipient in this type of reactions. We focus on reactions suggestive of being due to a type I hypersensitivity mechanism and other reactions such as delayed ones are not included in this review.

Systematic review, using the electronic searching in engine Pubmed/Medline until March 2021, was performed. We draw up an alphabetical list of excipients detailing the publications found about each of them. We highlighted the in vitro and in vivo tests used to confirm the diagnosis.

Aluminum

A case of anaphylaxis after a tetanus vaccination that includes aluminum as an excipient (Tetavax®) was reported in the literature. The patient previously described urticaria and angioedema after use of a large number of non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antihistamine preparations, methylprednisolone and colchicum. Most of these drugs were proven by provocation tests with good tolerance. A Finn Chamber® with pure elemental aluminum was placed on to the inner side of the forearm. An immediate urticarial lesion under the Finn chamber® that expanding up the entire arm was observed [5].

Benzyl alcohol

Turvey et al. described a patient with repeated anaphylactic reactions following vitamin B12 injections containing benzyl alcohol and no reaction to intranasal cyanocobalamin gel that does not contain benzyl alcohol. Skin prick-tests (SPT) with cyanocobalamin brand (1 mg/ml) and benzyl alcohol (0,9%) were negative but intradermal testing (IDT) with cyanocobalamin brand (0.01 mg/ml) and benzyl alcohol (0.009%) were positive [6].

Another case of vitamin B12 allergy due to benzyl alcohol sensitization has been previously reported with positive IDT (0.9%) [7].

One patient treated with benzyl alcohol-preserved cytarabine, vincristine, and heparin solutions developed an IHR on three separate occasions. The reaction was not seen on subsequent treatment with a non-preserved diluent. Hypersensitivity to benzyl alcohol was confirmed by IDT (0.9%) [8].

Benzalkonium chloride

Some cases of IHR to benzalkonium chloride have been reported with salbutamol nebulizer solution (Ventolin®) [9] eye drops [10] and xylometazolin hydrochlorid descongestant nose drops (Otriven®) [11] containing benzalkonium chloride.

SPT were carried out with three different concentrations of benzalkonium chloride (0.01% solution, 0.1% solution, 0.5% solution, each dissolved in H_2O). Mild reaction at 0.1% and very strong reaction at 0.5% was obtained [10].

ST with benzalkonium chloride should be done with caution because anaphylactic shock following an IDT with 1:10 salbutamol nebulizer solution containing benzalkonium chloride is reported [9].

Carboxymethylcellulose (CMC)

Several case reports of anaphylaxis due to CMC have been reported. The drugs involved in this type of severe reaction range from intramuscular [12–14], intraarticular [15–17] or intradermal [18] triamcinolone-containing injections to barium sulfate suspension [19] and eye lubricant solution [20]. A case of contact urticaria due to hydrocolloid dressings containing CMC has also been described in the literature [21].

The diagnosis of CMC hypersensitivity was reached by means of SPT and IDT with different dilutions; Li et al. used preservative free Carmellose eye drops 1% (10 mg/ml) (Moorfields Pharmaceuticals, London, UK) undiluted for SPT and 1:10 dilution for IDT [12]. Al Haditi et al. proposed IDT with CMD diluted at 0.001 and 0.01 mg/ml [16] and our working group are using Carmelosa Qualigen 5 mg/ml (Neuraxpharm, Spain) undiluted for SPT and diluted 1:100 and 1:1000 for IDT (0.05 and 0.005 mg/ml) [14] with good results.

In some reports, in vitro test as dot blot [20], basophil activation test (BAT) [13], enzyme-linked immunoassay (ELISA) [22], and in vitro histamine release [19] with CMC and with the suspected drugs, verified that reactions were induced by this excipient.

Carrageenan

Tarlo et al. reported a case of anaphylaxis during barium enema due to carrageenan allergy that showed positive SPT with 0.4% wt/vol sodium carrageenan and specific IgE antibodies (RAST) [23].

Cremophor

Cremophor EL (polyethoxylated castor oil, Kollipor EL) is prepared by reacting ethylene oxide with castor oil in a ratio of 35:1, so it is considered a PEG, PEG castor oil [24••]. Cremophor RH40 (macroglycerol hydroxystearate, Kolliphor RH40) instead is obtained by hydrogenated castor oil reacted with ethylene oxide at a molar ratio of 1:40 (hence the synonym PEG-40 hydrogenated castor oil) [25•]. Similarities among Cremophor EL, Cremophor RH40, and prolyoxyethylated oleic glycerides may be taken into consideration, suggesting different patterns of cross-reactivity [25•].

Anaphylactoid reactions induced by CrEL have been described. Manifestations vary from IHRs, postulating an IgE-mediated mechanism according to the positive of ST performed, to complement activation via the alternative pathway, leading into inflammatory mediators release [26]. Some authors suggested IgG antibodies involment according to Parusnitz-Kustner test and BAT [27], and other studies suggested direct histamine release by basophils or mast cells [27, 28].

IHRs have been described mostly induced by taxanes, and in most cases attributed to the vehicle used for administering them (Cremophor EL® and Tween 80, in Paclitaxel and Docetaxel respectively). The absence of Cremophor in some new formulations (naoparticule albumin-bound paclitaxel, Nab-paclitaxel) leaded in a lower incidence of this toxicity. Besides taxanes, IHRs to cyclosporine for intravenous infusion have been reported [27], and less frequently to the oral presentation/formulation [27, 29] (due to polyoxyl-5-oleate, the solvent of the oral solution).

The lack of standardization regarding diagnostic tests makes the demonstration of the underlying imunological mechanism challenging. In most of the cases reported, ST were not performed or exclusively SPT (Table 1).

Ethylenediaminetetraacetic acid (EDTA)

We only found a case in the literature of allergy to EDTA [33]. It is a patient who had a history of generalized urticaria after administration of a radiocontrast medium (RCM) (Isovue®) who developed anaphylaxis with subcutaneous injection of lignocaine (Lignospan Special®). IDT to calcium disodium EDTA 0.3 mg/ml was strongly positive and subcutaneous challenge with 0.1 ml and 0.5 ml resulted positive. IDT with undiluted RCM were positive in several RCM except for Iomeron 300®, the only RCM that does not contain EDTA. BAT was also positive with EDTA.

Table 1 Concentration of skin tests performed in previous studies/cases reported with Cremophor and drugs that contain it

Drug	Prick test dilutions (mg/ml)	Intradermal test dilutions (mg/ml)
Paclitaxel	1/10 (6 mg/ml) [30] 1/1 (undiluted, 6 mg/ml) [25•]	1/1000 (0,006) [30] 1/100 (0,06) [30] 1/10 (0,6) [30]
Cremophor EL	Undiluted (concentration not detailed) [31]	NP
PEG 35 castor oil (Cremophor EL, product number: 238470) *PEG 3350 Lax-A-Day® *PEG 3350 PegLyte®	1/1 (undiluted, 527 mg/ml) [32•] *PEG-35 diluted in etanol 50% to reach a concentration of 527 mg/ml. The mixture was vortexed until the solution was clear	NP
Cyclosporine (Neoral-Sandimmun® IV, 250 mg/5 ml, excipient Cremophor EL 650 mg/ml)	1/1 (undiluted) [25•]	1/10000 (0,065 mg/ml Cremophor EL) [25•]
Vitamin A Nepalm® (retinol palmitate 100,000 IU/2 ml, excipient Cremophor RH40 concentration not specified)	1/1 (undiluted) [25•]	1/10000 [25•]

NP not performed

FD&C yellow 6 (sunset yellow)

Taneja et al. reported a patient who developped generalized maculopapular rash after intake FD&C yellow 6 containing warfarina, ciprofloxacin and nitrofurantoin formulations with good tolerance to the same active ingredients without FD&C yellow 6 [34]. Diagnosis was made by clinical history [34].

Food proteins

Cow's milk protein (CMP)

Casein

Preparations of iron protein succinylate in drinkable vials: Ferplex®, Ferrocur®, and Lactoferrin® contain high amounts of casein [35]. A case of anaphylaxis after the intake of Ferplex® has been reported in a child previously diagnosed with cow´s milk allergy. The authors confirmed the diagnosis by SPT with undiluted Ferplex® and specific IgE determination by enzyme allergosorbent test (EAST) [36]. They also demonstrated the presence of casein in iron proteinsuccinylate by EAST inhibition.

Some lots of the Diphteria, Tetanus, and Pertussis vaccines (DTaP) that are processed in a broth derived from casein, can be contaminated by this protein. Kattan et al. identified 8 patients with severe milk allergy who had an anaphylaxis with booster doses of DTaP [37]. The authors identified casein in 8 lots of the vaccines (range 8 to 18 ng/mL). They concluded that residual casein in the vaccines might result in reactions for some highly sensitive patients with milk allergy.

Alpha lactalbumin (ALA) and bovine serum albumin (BSA)

It is reported a 10-month-old male patient with cow's milk allergy who had an anaphylactic reaction after receiving a single-component of measles vaccine (M-VAC®; Serum Institute of India, Hadapsar, Pune, India) with lactalbumin hydrolysate. The authors did not performed ST with the vaccine to confirm the diagnosis but at 12 months old, the child received the MMR (Priorix®; GlaxoSmithKline, Canada) vaccine, without any reaction [38].

Four children who had history of severe IgE-mediated allergy to cow's milk, suffered IHRs after vaccination with the oral polio vaccine (OPV, Trivalent vaccine Polioral®; Sclavo, Siena, Italy). Prick to prick with Sabin vaccine resulted positive. Levels of Sabin vaccine-specific IgE (ELISA) were increased and the authors confirmed the presence of ALA in the OPV by means indirect and competitive ELISA method [39].

IgE to BSA was seen in the majority of patients with cow's milk or beef allergy that have had hypersensitivity reactions to vaccines (measles, Japanese

encephalitis, rabies primary chick embryo, pentavalent, diphtheria and tetanus, and adult diphtheria and tetanus) in Sri Lanka. It was concluded that BSA might be the allergen responsible for the vaccine-associated allergic reactions [40].

Martín Muñoz et al. [41] studied the presence of egg and cow´s milk hidden allergens in 11 probiotics commercially available in Spain. SPT with the probiotics (20 mg/ml) were performed in children allergic to cow's milk, to hen's white egg, and controls. ELISA, SDS-PAGE immunoblotting, and inhibition studies were performed to demonstrate the presence of egg and CMP. CMP as BSA and ALA were detected in 10/11 probiotics, three over 2.5 mg/kg. Hen's egg white proteins were detected in 3/11 probiotics, only one had more than 2.5 mg/kg.

Lactose

Several cases of IHRs induced by Sol-Medrol® 40 mg (methylprednisolone sodium succinate) have been reported in cow's milk allergy patients [42–45]. There are 4 different doses of methylprednisolone sodium succinate, and lactose is found only in the 40 mg preparation (25 mg of lactose per vial). The diagnosis was confirmed by positive SPT and/or ID with Sol-Medrol® 40 mg used respectively at the concentration of 40 mg/ml and 0.4 y 4 mg/ ml [44, 45] being negative for Sol-Medrol® 125 mg [43].

The presence of CMP in ten different batches of Sol-Medrol ®40 mg was assessed by SDS-PAGE and immunoblotting methods [43] or ELISA assay [44]. A quantitative analysis of BLG in Sol-Medrol® 40 mg and 1 g of lactose found 112.5 ng of β-lactoglobulin per Sol-Medrol® 40 mg vial and 1.35 μg of BLG per gram of lactose [42].

Lactose was found to be the culprit of anaphylactic reactions after the inhalation of Inavir® (Laninamivir Octanoate Hydrate) to treat flu infection in an asmathic patient [46]. SPT and BAT resulted positive for Inavir® inhaler powder and lactose but negative for Laninamivir. The contamination of milk proteins in lactose excipient was demostrated by Western blotting using specific monoclonal antibody and patient's sera.

Another cases of refractory asthma exacerbation [47] and anaphylaxis [48] have been elicited by inhaling dry powder containing fluticasone/salmeterol (Advair Diskus, GlaxoSmithKline, Research Triangle Park, NC) in patients with milk allergy due to lactose contaminated by milk proteins.

Egg proteins

Lysozyme

IHRs with different drugs containing lyzozyme have been reported: nystatin and tetracycline vaginal suppository [49], mucolylic Leftose® [50], nasal decongestant containing neomycin, dexamethasone and chlorphenamine

[51], nasal decongestant Narlisim® [52] and Lizipaina® tablets (with bacitracin and papain) [53].

The diagnosis was performed by serum specific IgE (CAP System, Pharmacia, Uppsala, Sweden) against lysozyme and SPT with commercialized available extracts of egg white and lysozyme. In some cases, prick-to-prick with the drug containing lysozyme resulted positive [50, 52].

Ovalbumin (OVA)

The amount of OVA in residual medium of influenza vaccines is less tan 0.4 mcg per 0,5 ml dose and < 3 ng per 0.5 ml dose in the case of rabies vaccine, while higher amounts of egg protein have been found in yellow fever vaccine (< 4.42 mcg/ml) [54••].

Although anaphylaxis after influenza immunization is a theorical risk, different studies suggest that most individuals with egg allergy can be safely vaccinated with a single dose of the influenza vaccine, even those with severe egg allergy [55–59]. The authors do not recommend the use of ST because all of the patients tolerated the vaccine [55] neither IDT that were found to be irritative [54••]. They concluded that the vaccine can be administrated without supervision by an allergist [59].

Other similar studies are needed to investigate the tolerance of with rabies and yellow fever vaccines. Actually, the vaccination protocol with yellow fever vaccine proved to be safe for patients with a history of egg allergy [60, 61•]. Consists in perform SPT using undiluted vaccine and if negative, IDT with the vaccine diluted 1:100 in normal saline. If ST resulted negative, the patient can be vaccinated under medical supervision using 1 simple dose. If the ST are positive and the benefits to receive the vaccine outweight the risks, the dose of vaccine should administered in graded doses under observation [54••, 60, 61•].

Gelatin and α-Gal

The oligosaccharide galactose-α-1,3-galactose (α-Gal) is the cause of IHRs after exposure to some drugs that contain the molecule as part of its active ingredient such as the monoclonal antibody cetuximab [62], the Crotalidae polyvalent immune Fab antivenom [63•] and bovine-derived gelatine colloids [64]. This type of reactions has also been described with drugs and vaccines that contain gelatin as an excipient such as fenticonazole vaginal capsule [65] and varicela zoster and measles/mumps/rubella (MMR) vaccines [66, 67].

Gelatin is a bovine or porcine protein generated by partial hydrolysis and treatment of collagen and is used as a stabilizer in drugs and attenuated viral-containing vaccines such as Japanese encephalitis virus and MMR.

Gelatin can induce both vaccine [68] and drug allergy [69•]. There have been reports of anaphylaxis caused by gelatin capsules with include common oral cold medications (Advil Liqui-Gels®, Stona IB Gel®), and anesthetic suppositories (Chloral hydrate suppository®) [69•].

Although α-Gal has been recognized as part of the gelatin molecules responsible for some of vaccine´s allergy [66, 67], a case of zoster vaccine anaphylaxis has been reported in a patient who had IgE to gelatin but not to α-Gal [70].

Sakaguchi et al. identified the alpha 2 chain of type I collagen as the causative agent in children who showed anaphylaxis to bovine gelatin containing live virus vaccines [68].

For gelatin allergy diagnosis, bovine gelatin-derived colloids undiluted as Haemaccel® and Gelofusine®, with 35 and 40 mg/ml gelatin respectively, have been used for SPT and IDT [64]. We also can perform a determination of IgE antibodies to porcine and bovine gelatin and bovine thyroglobulin α-gal using serum specific IgE test commercially available. In α-gal allergic patients ST with gelatin-derived colloids showed strong correlation with anti-α-Gal IgE measurements [64]. Cetuximab (Erbitux, Merck S.L.) can also be used to perform ST and BAT with high sensitivity and specificity [71]. The concentrations proposed are 5 mg/mL for SPT and 5 μg/mL for IDT [71].

SPT using the undiluted vaccine an IDT with the vaccine diluted 1:100 in normal saline seem to be non irritative and support the vaccine allergy diagnosis [54••].

Hexylene glycol

A case of contact urticaria, angioedema, and dyspnea following the application of a topical mometasone furoate cream (Elocom®), caused by hexylene glycol, has been reported. A positive reaction was present to pure hexylene glycol at 1 and 10% concentrations by prick and rub tests. No cross-reactivity to propyleneglycol or PEG was detected [72].

Hydroxypropyl methylcellulose

A case of anaphylaxis to hydroxypropyl methylcellulose (HPMC) on 2 different occasions during cataract surgery was reported due to Ocucoat® and Xylocaine gel®. In the case of Xylocaine gel®, HPMC was an excipient but in Ocucoat® was the active ingredient. SPT were positive for Ocucoat gel® (with 2% HPMC) [73].

Macrogols

Macrogols, also named PEGs, constitute a large family of hydrophilic polymers derived from ethylene oxide [4••, 67, 74] that includes PEGs of varying molecular weights (MW) and some other related molecules, such polysorbates (PS) [4••, 67].

They are commonly used as excipients in many different products like pharmaceuticals and cosmetic but also as active ingredients in laxatives and bowel preparations and as part of the PEGylation process of several drugs [4••, 74, 75••, 76•]. Due to their structural similarity, cross-sensitization between PEGs and PS has been described [67, 77–79], even though its clinical relevance has not been clearly assessed [4••, 74, 75••, 80•, 81••].

Interest in macrogols has notably increased lately due to their role in the reported reactions with COVID-19 vaccines. Nevertheless, they are so widely distributed that they have been related to IHRs of diverse severity for years.

PEG 8000 and 6000 were found to be the culprit agents in anaphylactic reactions with an ultrasound gel [82], and with a povidone-iodine gel [77] and PEGs with MW between 3000 and 6000 in IHRs after oral intake of nonrelated drugs [78, 79, 83•, 84]. Anaphylaxis due to PEG 3350 and 4000 with laxative agents during bowel preparation [83•, 84, 85], after injection of corticosteroids [86] and ultrasound contrast agent [87] have also been described. At times, patients reported previous IHRs to products containing macrogols [77–79, 84, 85].

As known, mRNA vaccines against SARS-CoV-2 Moderna® and Pfizer® BioNTech contain PEG 2000. ST with PEGs in the diagnosis of COVID-19 vaccines allergy is controversial. While some reports demonstrate the involvement of this excipient in IgE-mediated reactions with mRNA COVID-19 vaccines [87, 88], a recent published meta-analysis underlines the poor sensitivity of ST and suggests against routinely performing them [81••].

PS 20 and PS 80 are common excipients in biological drugs and they have been involved in IHRs after the administration of several monoclonal antibodies [89, 90]. PS 80 has also been related with IgE-mediated reactions with corticosteroids [91], etoposide [92], quadrivalent human papillomavirus vaccine [93], erythropoietin, and darbepoietin [94].

One of the most challenging points in the diagnosis of macrogol allergy is the lack of agreement on how to perform ST and, undoubtedly, there is a need to create standardized protocols with validated concentrations.

In literature, in those cases where diagnosis was reached by ST with macrogols, authors use different concentrations [75••].

We have a wide experience in testing PS 80 at concentrations proposed by Palacios et al.—SPT at 0.4 mg/ml and IDTs at 0.004 mg/ml and 0.04 mg/ml—and we can assure that they are non-irritating.

According to the drug allergy committee of the Spanish Society of Allergology and Immunology (SEAIC) and following the diagnostic approach recommended by Sellaturay et al. and Palacios et al. we suggest a testing protocol with macrogols (Table 2). We have found those concentrations non-irritanting. Nonetheless, further studies are needed to assess their sensitivity.

In certain cases, it may be advisable to perform ST with higher MW PEGs, as they can be diagnostic when lower MW PEGs test negative [74, 76•, 80•, 83•]. Systemic reactions with IDTs with PEGs have been described. Hence, it is essential to perform stepwise SPT before carrying out IDT [76•, 80•, 83•].

Table 2 Proposed concentrations for skin testing with macrogols [91, 95•]

	PEG 1500 (Roxall)	PEG 2000	PEG 3350 (Movicol ®)	PEG 4000 (Casenlax ®)	PS 80
Prick-test	1 mg/ml 10 mg/ml 100 mg/ml	1 mg/ml 10 mg/ml 100 mg/ml	2.5 mg/ml 25 mg/ml	2.5 mg/ml 25 mg/ml	0.4 mg/ml
Intradermal test	0.01 mg/ml	0.0001 mg/ml 0.001 mg/ml	0.00025 mg/ml 0.0025 mg/ml	0.00025 mg/ml 0.0025 mg/ml	0.004 mg/ml 0.04 mg/ml

Mannitol

IHR to intravenous mannitol are usually attributed to the hyperosmolar properties, being able to trigger a non-specific mast-cells or basophils degranulation produced by non-immunologic mechanism [96, 97].

There are some reports that show that mannitol can induce a true IgE-mediated reaction: two cases of allergy to mannitol in intravenous paracetamol (Perfalgan®) [98], a case with granular effervescent paracetamol (Tachipirina®) [99] and another one with the intake of a chewable tablet of cisapride (Cisapid MPS®) [100]. Mannitol SPT resulted positive with 1% w/v (10 mg/ml) concentration [100] in some reports. Other researchers obtained negative SPT with mannitol 20% but IDT to manitol diluted at 1:1000, 1:100 and 1:10 gave a positive response [98, 99].

Metacresol

Wheeler et al. documented a case of an allergic reaction to the metacresol component of different insulins [101]. The patient suffered pain, localized erythema with skin breakdown occurring within 5 min after the injection that evolved into multiple healing abrasions at the different puncture points. Subcutaneous testing resulted positive with all available insulin and metacresol was the only excipient common to all. Since it was not available commercially for testing, subcutaneous testing was performed with Lilly™ "saline" penfills that containing metacresol as the only significant ingredient eliciting an identical positive reaction.

Poloxamer 238

A clinical case of anaphylaxis due to poloxamer 238 has been described in literature during a radiological examination with intravenous injection of a marker with Tc99m (Nanocoll®) that contains this excipient. SPT and

IDT (1:1000) with poloxamer 238 were positive and negative in 5 controls. A histamine release test was also positive [102]. As poloxamers are block copolymers of PEG and polypropylene glycol, cross-reactivity between poloxamers and macrogols could potentially occur.

Povidone (polyvinylpyrrolidone PVP).

Anaphylaxis due to povidone iodine have been reported after intravenous administration of paracetamol that contains this excipient [101]. Another cases of anaphylactic reaction after oral intake of flubendazole suspension (Fluvermal®) [103], acetaminophen-containing tablets (Doregrippin®) [104], intraarticular paramethasone acetate [105], prednisolone oral solution (Estilsona®) [106], and loteprednol eye drop [107] have also been reported.

PVP allergy diagnosis was confirmed in some cases by a positive SPT with 5% povidone iodine (aqueous solution) diluted 1:100 with normal saline (0.5 mg/ml) [108] or betadine solution without dilution (100 mg/ml or 75 mg/ml) [106, 107]. Other authors demonstrated specific IgE antibodies against PVP using a dot blot technique [104].

Protamine

Several cases of severe IHRs after subcutaneous injections of neutral protamine Hagedorn (NPH) have been described [109, 110, 111]. Some patients have also past history of anaphylactic shock after intravenous administration of protamine sulfate used for heparin reversal [109, 110].

Diagnosis was reached by means of positive serum specific IgE and ST for protamine and protamine containing insulin and negative to protamine free insulin. Currently, we have available the comercial technique of InmunoCAP® for protamine and insulin specific IgE determination.

Blanco et al. proposed to carry out SPT with different insulins at a concentration of 40 UI/ml and with protamine sulfate at 10 mg/ml. They also perform ID with serial tenfold dilutions of insulins and protamine starting with a 1:100,000 dilution, reaching a maximum of 0.4 UI/ml for insulins and 0.1 mg/ml for protamine [112].

Tromethamine or trometamol

We only have found a case of an anaphylactic reaction to Trometamol on the literature [113••] induced by the parenteral administration of gadoteridol (Prohance®).

SPT with undiluted gadolinium contrast agents and IDT in the range 1:1000, 1:100, and 1:10 dilutions were performed. SPT and IDT with

trometamol diluted to same concentration as that contained in the index gadolinium contrast agents were also performed. They resulted negative to gadoterate meglumine (Dotarem®), the only one that does not contain Trometamol and positive at 1:100 concentration, with gadoteridol (Prohance®) and gadobutrol (Gadovist®), and at 1:1000 to trometamol.

With the recent appearance of COVID 19 vaccines, and being Trometamol one of the excipients, it is also suspected to be the responsible for some of the vaccine reactions described [114••].

Zinc

A patient developed an IHR after the administration of NPH, detemir and rapid insulin with positive SPT to zinc chlroride 5 µg/ml (10, 20 and 40 fold diluted). He tolerated zinc-free glulisine insulin [115].

Another case of IHR with Monotard® (porcine monocomponent insulin), Monotard HM® (human semisynthetic monocomponent insulin) was described. IDT were negative to bovine, porcine, and human insulin, but strongly positive to diluting medium for Monotard and to zinc acetate (dilutions not detailed). The patient was completely free from allergic manifestations after switching to Actrapid HM® (human semisynthetic monocomponent insulin) [116].

We have also found two reports of cutaneous generalized allergy due to the use of porcine insulin (Monotard®) and also human Protaphane ® and Humulin NPH®. IDT were negative for insulin but strongly positive for diluting medium for Monotard, zinc acetate and protamine (dilutions not detailed) [117, 118].

Conclusion

Excipients in drug and vaccine formulations represent a true puzzle for allergists. At a first sight, the active pharmaceutical molecule is usually considered the responsible agent for a IHR, but all vaccine and drug components should be considered as potential triggers of an allergic reaction. For this reason, a careful investigation is required for the correct identification of the culprit agent.

We also would like to highlight the significance of clear labelling of all ingredients including excipients in pharmaceutical preparations and reiterate the importance and value of an allergological work-up in order to provide planning advice to avoid future reactions.

For some excipients such as gelatin, alpha-gal, and food-derived excipients, we have in vivo and in vitro diagnostic tests with high sensitivity and specificity, but for most excipients, we must continue working to improve diagnostic procedures.

Declarations

Conflict of Interest
Mónica Venturini Díaz declares that she no competing interests. Vidal Irene declares that she no competing interests. D'Elia Diana declares that she no competing interests. Alarcón Eladia declares that she no competing interests.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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