Place of Excipients in Systemic Drug Allergy

Annick Barbaud, MD, PhD*

KEYWORDS

• Excipients • Sulfites • Carboxymethylcellulose • Sodium benzoate • Vaccines • Insulin

KEY POINTS

- Overdiagnosis of vaccine allergy is common and is considered as a major public health problem.
- The diagnosis of allergy to vaccine is complex and is often retained due to fear of severe anaphylactic reactions. However, most of the patients labeled as allergic to a vaccine tolerate a subsequent injection of the vaccine without clinical reaction. This is particularly the case of patients developing local reactions or delayed benign skin rashes.
- Regarding patients with a history suggestive of an immediate IgE-mediated hypersensitivity, a complete workup is mandatory. It will be primarily based on skin tests and/or specific IgE measurements.
- In the vast majority of cases, the vaccines can be administered using adapted protocols, even if the allergy tests are positive.
- Some vaccines' administrations carry a relatively high risk of severe anaphylactic reactions and should always be performed by well-trained physicians and emergency equipment must be readily available.

An excipient is an inert substance added to a drug to change dissolution or the kinetics of absorption, improve stability, influence palatability, or create a distinctive appearance. Also called additives, they are preservatives, emulsifiers, stabilizers, or thickeners. Drug hypersensitivity reactions (DHR) to them may lead to a false-positive diagnosis of DHRs to the specific active principle.

Allergic contact dermatitis to drug excipients has been more thoroughly studied (see article in this issue by Goossens) than DHRs related to excipients in drugs administered systemically. We only discuss the most frequent of the latter.

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Dermatology and Allergy Department, Brabois Hospital, University Hospital of Nancy, Lorraine University, Rue du Morvan, Vandoeuvre les Nancy 54500, France
* Dermatology Department, University Hospital of Nancy, Pole des Specialités Medicales, Brabois Hospital, Universite de Lorraine, 6 Rue du Morvan, Vandoeuvre les Nancy 54500, France.
E-mail address: a.barbaud@chu-nancy.fr

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BENZYL ALCOHOL

When used as a preservative, benzyl alcohol can cause sensitization by contact with topical ointments but also by a systemic way. Two case reports illustrate this. Shmunes[1] has reported a case of allergy to benzyl alcohol used as a preservative in a solution of sodium tetradecyl sulfate, an agent used in sclerotherapy for varicose veins. A 16-year-old girl had immediate sensation of substernal burning and pleuritic pain associated with pruritus of the arms and legs after cyanocobalamin injections, with a vitamin B12 preparation containing benzyl alcohol (0.9%).[2] Prick test results were negative, but intradermal tests gave immediate positive results in testing 3 different cyanocobalamin brands containing benzyl alcohol and also with benzyl alcohol diluted at 0.009%.

CARBOXYMETHYLCELLULOSE

Carboxymethylcellulose (also called *carmellose* or *croscarmellose*, *sodium carboxymethylcellulose*, and *E466*) is a hydrophilic derivative of cellulose used in injectable preparations as a suspending agent to promote solubilization of compounds with poor water solubility; it is also present in tablets as binder, glidant, and antiadherent, as active principle in bulk laxatives and as an additive in food products. The immediate hypersensitivity of croscarmellose is primarily reported after intra-articular infiltration of corticosteroids[3–7] but also with a generic furosemide.[8]

In immediate reactions to injectable drugs containing carboxymethylcellulose, it is reported that oral administration of carboxymethylcellulose is well tolerated owing to its weak absorption through the digestive tract.[3,9]

However, carboxymethylcellulose anaphylaxis has been reported after contact with gut mucosa during barium enema.[10,11]

In immediate hypersensitivity to carboxymethylcellulose, prick tests and intradermal tests can have positive results, and immunoglobulin E (IgE) has been identified using dot-blot analysis but could not be specific.[10,11] Bigliardi and colleagues[7] have emphasized the value of the cellular antigen stimulation test.

For patients with a suspicion of carboxymethylcellulose sensitization, it is recommended to perform prick tests with carboxymethylcellulose, then, to determine if there is an oral tolerance to carboxymethylcellulose, to continue with an oral provocation test. Prick tests can be done with carboxymethylcellulose at 5 mg/mL[7] and can be positive at lower concentrations.[4]

Positive results have been reported using intradermal tests (IDT) with carboxymethylcellulose at 0.005 or 0.01 mg/mL.[7,10,11] Unfortunately, currently, we do not have any more available injectable forms of carboxymethylcellulose for performing IDT. Therefore, performing IDT with the responsible drugs containing carboxymethylcellulose is the only alternative.

Bigliardi and colleagues[7] suggest performing an oral provocation test with carboxymethylcellulose to exclude a reaction to small oral doses of this widely used carbohydrate. But patients allergic to carboxymethylcellulose usually do not react to the oral application of a small amount of carboxymethylcellulose typically present in food and tablets.

Three cases of systemic delayed hypersensitivity to carboxymethylcellulose have been reported with maculopapular rash.[12] This delayed sensitization can mimic multiple sensitizations to different drug classes. In such cases, prick tests and intradermal tests can have positive results on their delayed readings, there is no oral tolerance to carboxymethylcellulose, and there are no cross-reactions with hydroxypropylcellulose.

DYES

The relevance of hypersensitivity to dyes among all drug hypersensitivities remains unclear. According to Bhatia,[13] among 2210 patients exposed to tartrazine-containing drugs, 83 (3.8%) had adverse reactions, and the symptoms subsided within 24 to 48 hours of stopping the drug. None of the patients showed allergy to non–tartrazine-containing brands. Swerlick and Campbell[14] reported on 11 patients with chronic, unexplained pruritic skin disorders that have responded to medication changes centered around avoidance of dyes, particularly FD&C Blue No. 1 (bright blue) and Blue No. 2 (indigo carmine). Therapies were switched back to the lighter-colored tablets or a dye-free liquid form (doxepin), and the dermatitis promptly resolved.

Twenty-four hours after beginning an iron oral treatment (ferrous sulfate, Sunset Yellow FC&C No. 6 (E110 = orange disperse 3), erythrosine (E127), titanium dioxide (E171), and methyl methacrylate), a 43-year-old woman had a severe facial erythema with itching and skin edema.[15] It could be considered a flare up of a previous professional contact dermatitis. After patch tests, slight facial erythema was observed 6 hours after the application, and the patient had positive patch tests for orange disperse 3 (Sunset Yellow), para-phenylenediamine, and nickel sulfate after 48 hours. The authors supposed that she had become sensitized to these substances during her former occupation as a hairdresser. A single-blind, placebo-controlled oral challenge was made, with ferrous sulfate eliciting facial itching and erythema and no reaction with ferric propionate.

On the other hand, yellow dye tartrazine was supposed to be a potential cause of exacerbations of asthma, allergic rhinitis and urticaria in atopic patients. But, in 26 atopic patients, a double-blind, placebo-controlled, crossed-over challenge with 35 mg of tartrazine was done, and no significant cutaneous, respiratory, or cardiovascular reactions were seen when compared with placebo.[16]

In a unicenter, retrospective study, 102 subjects with suspected tartrazine-induced acute urticaria/angioedema had a placebo-controlled challenge with 5 mg of tartrazine.[17] Among them, only one patient had a positive oral provocation test result. The authors suggested that all patients who have had adverse reactions that could be attributed to tartrazine should also be carefully evaluated for other possible causes.

In case of hypersensitivity reactions supposedly caused by dyes, only a provocation test can prove the responsibility of these excipients.

POVIDONE

Povidone (PVP, polyvinylpyrrolidone) is a mixture of synthetic polymers with molecular weights between 10,000 and 70,000 Da, comparable to those of the plasma proteins.

Michavila-Gomez and colleagues[18] reported one case with an anaphylactic reaction occurring in a 4-year old boy after using a prednisolone oral solution with povidone. The result of prick test with pure noniodinated povidone (25 mg/mL) was positive, and the result of oral provocation test carried out with methylprednisolone at 20 mg was negative. A relapse occurred when the child orally received cefuroxime axetil with povidone K30. From the literature, the authors collected other cases in children caused by PVP associated with flubendazol or in a formulation containing paracetamol. In adults, there are cases involving the intra-articular administration of drugs containing corticosteroid and PVP or after the administration of contrast medium containing PVP. One case with acetaminophen-containing tablets was also reported by Rönnau and colleagues.[19]

Methods for testing PVP are not standardized. There are some reports with positive results in performing prick tests with PVP, with solution of povidone iodine, or with the formulation of the responsible drug and another formulation with another excipient,

positive scratch test, or intracutaneous provocation tests with injectable forms of the responsible drugs.

SODIUM BENZOATE

Sodium benzoate (E211) has been implicated in the onset of some types of food-induced asthma, urticaria, or anaphylaxis. It is found in anticough syrups, vitamin preparations, heparin, or antibiotic syrups.

Recently, a high frequency of sodium benzoate hypersensitivity has been reported in children with cutaneous reactions occurring during the amoxicillin plus clavulanic acid suspension intake.[20] Single-blind oral provocation tests with amoxicillin plus clavulanic acid, sodium benzoate, and placebo were performed in 89 children with cutaneous reactions while taking the antibiotic suspension and in 20 sex- and age-matched controls who had chronic idiopathic urticaria. Sodium benzoate was administered at 2 doses up to 150 mg and 250 mg depending on the body weight (15–40 kg or 41–50 kg). Ten children (11%) had reactions after the provocation test with sodium benzoate with tolerance to amoxicillin plus clavulanic acid, and 3 children had positive reactions to both the excipient and the active drug. The provoking cumulative dose of sodium benzoate was usually 150 mg (9 of 13), and 4 patients had a positive response to 50 mg of sodium benzoate.

Some investigators suggest that because benzoates are structurally similar to acetyl salicylic acid (aspirin), they may act on eicosanoid production, so Mori and colleagues[20] suggest that it would also be good to check acetyl salicylic acid tolerance in children reacting to sodium benzoate. These results suggest that benzoate hypersensitivity should be investigated in children manifesting reactions to drugs containing it, once an allergy status in relation to the antibiotic is excluded or confirmed.

SULFITES

Sulfites are sulfur dioxide salts that are widely used as antioxidants in food and drugs. In the pharmaceutical industry, they are mainly used in local anesthetic solutions, including those containing epinephrine and most of the available solutions of epinephrine; in some injectable antibiotics, corticosteroids, dopamine, isoproterenol, and propofol; and in ancient bronchodilator inhalational agents. By systemic exposure, most adverse reactions have been reported with sulfites contained in food. They occur primarily in asthmatic patients and induce exacerbation of asthma, pruritus, urticaria, angioedema, flush, or even hypotension.

With drugs, sulfites have been found to cause paradoxical worsening of asthma exacerbations when old bronchodilator inhalational agents were used after injection of local anesthetic agents containing sulfites or epinephrine. They are suspected to be responsible for angioedema, urticaria, and for the reactivation of an occupational-related contact dermatitis (flare up of a contact allergy).[21]

A few cases of asthma exacerbations have been reported caused by sulfites in drugs such as corticosteroids, local anesthetics, gentamicin, metoclopramide, doxycycline and vitamin B complex, or propofol.[22,23]

The mechanism involved in adverse reactions after a systemic exposure to sulfites remains unclear and may be a multifactorial process: inadequate sulfite oxidase activity, non–IgE-induced mast cell degranulation. Prick tests and intradermal tests with sulfite have no value; that of oral challenge tests is better but is not well standardized and potentially dangerous in sulfite-sensitive asthmatics. Recently, it has been observed in vitro that sodium sulfite significantly and dose-dependently suppressed Th1-type immune response, which could play a central role in the

precipitation of allergy symptoms by modulating cytokine profiles toward a Th2-type pattern.[23]

Sensitization to sulfites contained in drugs seems to be rare and must be considered mainly in patients with asthma. However, provocation test with the suspected drug and with sulfites can show hypersensitivity to this excipient. As emphasized by Vally and colleagues,[22] most of the commercially available preparations of adrenaline contain metabisulfite. However, even in patients with serious sulfite sensitivity, the benefit from adrenaline is considered to outweigh the risk of sulfite exposure associated with use of adrenaline in an emergency.

NONIONIC POLYETHOXYLATED SURFACTANTS

Nonionic polyethoxylated surfactants, polysorbate 80 (PS80, E433, Tween 80, polyoxyethylene sorbitan monooleate), and Cremophor-EL (CrEL = polyoxyethylated castor oil in 50% ethanol) activate the complement system in vitro in normal human serum and plasma. They are more efficient reactogens than their structural homolog, Tween-20. Cremophor-EL and Tween-80 activate the complement system in similar extent. Therapeutic side effects, such as acute hypersensitivity and systemic immunostimulation, caused by intravenous medicines containing polyethoxylated detergents, can be attributed to complement activation-derived inflammatory mediators.[24]

Serious forms of hypersensitivity reactions have been reported several medicines containing nonionic polyethoxylated surfactants, including paclitaxel with CrEL, docetaxel, or erythropoietin with PS80.[25,26] Premedication regimens and longer infusion times lowered the incidence of reactivity. If tolerance remains poor, rapid desensitization by a standardized 12-step protocol has been reported as safe and effective.[26]

EXCIPIENTS IN VACCINES

Aluminum-Induced Granuloma

Sulfate and aluminum phosphate hydroxide are used as adjuvants in numerous vaccines and in solutions for subcutaneous allergen immunotherapy. Aluminum sensitization caused by vaccinal solutions results in the appearance of nodules at the injection site, which usually regress after a few weeks or months.[27,28]

In some cases, the granulomas persist for years. These cases have been reported after vaccination or subcutaneous allergen immunotherapy.[27] These patients can experience flare ups at the nodule site, especially if they are exposed to aluminum again, either by injection of a solution with aluminum or by using antiperspirants containing aluminum salts.

Histologic assessment is not necessary because, when performed, a poorly circumscribed infiltration of lymphocytes into the hypodermis can be observed, sometimes reaching the deeper dermis, with a crown shape circling the cicatricial sclerosis. Staining with pentahydroxyflavone can be used to detect fluorescent intramacrophagic aluminum particles.

Diagnostic confirmation can be made by revealing the sensitization to aluminum by positivity to the patch test with an aluminum extract or in using an empty aluminum-made Finn Chamber cupule. Patch tests with aluminum extracts are inconsistently positive in patients who have granulomas at the site of injection.

In sensitized subjects, the use of antiperspirants, deodorants, or topics containing aluminum salts should be discouraged. Subcutaneous allergen immunotherapy with aeroallergens containing aluminum is contraindicated. For vaccinal solutions that do

not exist without aluminum, the injections should be deep enough to limit the exposure to aluminum.[27,28]

Antibiotics in Vaccines

Several vaccines are subjected to processing with antibiotics during the manufacturing process. Although these antibiotics (neomycin, streptomycin, kanamycin, Aureomycin) may be present in a vaccine solution, they were never implicated in vaccine allergy (see Caubet-Ponvert in this issue).

Egg Protein and Vaccines

Some vaccinal preparations, such as measles, seasonal flu, yellow-fever, rabies, tick-borne encephalitis and some influenza A H1N1 vaccines, are made on chicken egg embryos or fibroblasts of chicken embryos.[27]

For the flu vaccine, the prick test is of no interest when determining if tests for vaccinal solutions help in patients with egg allergies.[29] In patients with serious anaphylactic reactions to egg proteins (asthma or anaphylactic shock), some investigators proposed carrying out the vaccination through a 2-step protocol under hospital supervision: a first injection at 10% of the dose, and 30 minutes later, if well tolerated, a second injection at 90%.

For any patient suspected to be allergic to eggs, the following points should be taken into account:

- If eggs are consumed and well tolerated: it is possible to vaccinate without any particular precaution
- If egg consumption leads to minor allergic manifestations: vaccinate and follow up after 30 minutes
- If there is a suspicion of egg allergy but eggs have never been consumed: perform a prick test with egg proteins and adapt the vaccine to the intensity of the response to these tests
- In case of proven egg allergy (positive prick tests), and severe or uncontrolled asthma or history of anaphylaxis: the risk-to-benefit ratio should be evaluated, the maximal ovalbumin concentration authorized in the vaccinal solution should be verified, and vaccination should be performed under hospital supervision, possibly by a 2-step protocol (10%, and 30 minutes later, 90%).

Contamination from the Media Used for Recombinant Vaccines

Engerix B is the only hepatitis B vaccine prepared from *Saccharomyces cerevisiae.* A female patient with a history of food allergy to yeast suffered an anaphylactic shock with the first injection of Engerix B.[27] Prick tests were positive with the vaccine and yeasts, which implied that the triggering agents were anti-*Saccharomyces* IgE. Vaccine adverse effects are rare in yeast-sensitive individuals.[30]

Gelatin

This protein derivative of animal collagen, the component most widely used in manufacturing drug capsules, is sometimes used as an excipient in injectable solutions. Gelatin is well tolerated when used as an excipient, unlike what is observed when it is used as a plasma expander. Contained in some vaccines, gelatins induced an anaphylactic reaction with antichickenpox injection in a 4-year-old child who had a previous food allergy to gelatinous candies; an anaphylactic reaction has also been seen in some cases with the mumps-measles-rubella vaccine.[27,31,32] Among 366 Japanese patients who presented hypersensitivity reactions after

mumps-measles-rubella vaccination with 0.2% gelatin, anti-gelatin IgE was detected in 25 of the 27 (93%) subjects with anaphylaxis.[32]

EXCIPIENTS IN INSULIN

The prevalence of allergic reactions to insulin products appears to be approximately 2%, and less than one-third of these events has been considered related to the insulin itself. Other reactions occur because of the preservatives added to insulin, including metacresol, protamine, and zinc.

Metacresol

Localized reactions at the injection site can be accompanied by positive patch tests to metacresol.[33,34]

Three cases of delayed-type hypersensitivity reactions to meta-cresol were reported with systemic symptoms, including nausea, headache, sweating, and diarrhea. In only one of the 3 cases erythematous burning lesions at the injection sites were present on the day after the subcutaneous administration of insulin.[35] Delayed reactions improved after they were treated with human insulin free of metacresol.

Protamine

Protamine is a low-molecular-weight polycationic protein purified from testes and sperm of salmon. It is used in the treatment of cardiovascular disorders to neutralize the effects of heparin and also as an adjuvant in insulin. In this latter use, it could induce localized delayed reactions or urticaria. Protamine reactions could be triggered by allergic or nonimmunologic mechanisms through an activation of the classical complement pathway.[35,36]

Chu and colleagues[36] reported one case of a fatal allergic reaction possibly associated with protamine administration in a patient with a history of allergy to fish and to protamine-containing insulin. Some investigators have recommended the dose of antiprotamine IgE.[37]

Zinc Oxide

Delayed-onset allergic reactions localized at the site of insulin injection or systemic urticaria associated with zinc have been reported.[38] In a patient who had generalized urticaria with face edema and dyspnea after each injection of zinc-containing insulin, a prick test done with zinc chloride (5 mg/mL), displayed positive results with a local reaction and also a laryngeal tickling and a transient urticaria.[39]

SUMMARY

Hypersensitivity reactions to excipients contained in drugs are rare but can be severe or confusing. With regard to generic versus brand drug, often the ingredients are different; for each DHR, we recommend that the physician exercises caution in considering which brand drug or generic was administered and in listing all medicine components and not only the active drug.

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