

Place of Excipients in Systemic Drug Allergy



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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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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. Shmunes¹ 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 corticosteroids³⁻⁷ 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 colleagues⁷ 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/mL⁷ 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 colleagues⁷ 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.

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