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Unexpected outcome (positive or negative) including adverse drug reactions

Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80

Iuliana Badiu,[1] Massimo Geuna,[2] Enrico Heffler,[1] Giovanni Rolla[1]

[1]Allergy and Clinical Immunology, University of Torino and AO Ordine Mauriziano, Torino, Italy;
[2]Laboratory of Immunopathology, AO Ordine Mauriziano of Torino, Torino, Italy

Correspondence to Professor Giovanni Rolla, grolla@mauriziano.it

Summary

A 17-year-old girl reported generalised urticaria, eyelid angioedema, rhino-conjunctivitis, dyspnoea and wheezing 1 h after third intramuscular administration of quadrivalent human papilloma virus vaccine (Gardasil). She was treated with antihistamine, and corticosteroids with prompt relief of rhinitis and dyspnoea, while urticaria and angioedema lasted 24 h. Intradermal test with Gardasil, which contains polysorbate 80 (PS80), resulted positive, while skin tests with the bivalent vaccine were negative. Prick test performed with PS80 resulted positive in the patient and negative in ten healthy controls. The CD203 basophil activation test result was negative for PS80 at all the tested dilutions and specific IgE was not found. As flu vaccine was recommended, the authors skin tested two flu vaccine, one containing PS80 (Fluarix, GSK), which resulted positive and another flu vaccine with no adjuvant or preservative (Vaxigrip, Sanofi Pasteur MSD), which gave negative results. The patient then received Vaxigrip without adverse reactions.

BACKGROUND

True hypersensitivity to the quadrivalent human papillomavirus vaccine is uncommon, anaphylaxis being estimated at 1/190000 injections.[1] Hypersensitivity reactions may occur toward active ingredients, and to different excipients that are necessary to preserve and stabilise the product. These substances are commonly considered inert molecules and therefore are not believed to be potential causes of adverse reactions. However, they also may induce biological responses, as it is shown in the case we describe, which is the first case of allergic reaction to a vaccine due to polysorbate 80 hypersensitivity.

CASE PRESENTATION

A 17-year-old girl reported generalised urticaria, eyelid angioedema, rhinitis and conjunctivitis, dyspnoea and wheezing 1 h after third intramusclar administration of quadrivalent human papillomavirus vaccine (Gardasil). She was treated with antihistamine, and corticosteroids with prompt relief of rhinitis and dyspnoea, while urticaria and angioedema lasted 24 h. Medical history was significant for seasonal rhinitis due to grass sensitisation, autoimmune thyroiditis on substitutive therapy and type 1 diabetes mellitus on four daily insulin injections.

Skin prick with 1:1 and intradermal tests with 1:1000 and 1:100 dilutions were carried out for both the quadrivalent human papillomavirus and the bivalent human papillomavirus vaccines. Quadrivalent vaccine contains polysorbate 80 as excipient, and both vaccines contain aluminium hydroxide as adjuvants, coupled with O-desacyl-4'- monofosforyl lipide A in the bivalent vaccine. Protein vaccine L1, contained in Gardasil, is obtained by recombinant DNA technique using *Saccharomyces cerevisiae* yeast. We measured skin weals 20 min after skin testing and considered diameters of 3 mm or more above the saline control as a positive result.

Intradermal test with 1:1000 dilution of the quadrivalent vaccine resulted in a positive response (weal diameter 10 mm), while all the skin tests with the bivalent vaccine gave negative results. Prick test with baker's yeast (*Saccharomyces cerevisiae*, Lofarma SpA, Milan, Italy) was negative. To establish non-irritating concentrations of polysorbate 80 for skin tests, ten healthy controls were prick and intradermal tested with polysorbate 80, and showed negative responses up to a 1:10 dilutions. In the patient prick test performed with polysorbate 80 (Tween 80; Merck, Darmstadt, Germany) at 1:1000 dilution resulted in a positive response after 20 min (weal diameter 8 mm), followed by pruriginous erythema limited to the chest, which vanished 30 min after antihistamine. Skin tests confirm the role of polysorbate 80 in the development of allergic reaction in our patient. The CD203 basophil activation test result was negative for polysorbate 80 at all the tested dilutions and specific IgE against polysorbate was not found.

As flu vaccine was recommended in our diabetic patient, we skin tested (undiluted prick and 1:1000 and 1:100 dilution intradermal tests) two flu vaccines, one containing polysorbate 80 (Fluarix, GlaxoSmithKline S.p.A., Verona, Italy), which resulted in a positive response 20 min after 1:1000 intradermal test (weal diameter 10 mm), and another flu vaccine with no adjuvant or preservative (Vaxigrip, Sanofi Pasteur MSD SpA., Roma, Italy), which gave negative results. The patient then received Vaxigrip without adverse reactions.

OUTCOME AND FOLLOW-UP

The patient received Vaxigrip, which does not contain polysorbate, without adverse reactions.

DISCUSSION

Polysorbate 80 (also known as polyoxyethylene-20-sorbitan mono-oleate, Tween 80 and E-433) is an ethoxylated

hydrophilic non-ionic synthetic compound derived from ethylene oxide, sorbitol and oleic acid. It is used as surfactant, stabiliser and emulsifier in the composition of cosmetics, industrial detergents and in a wide variety of topical, oral and parenteral drugs. Polysorbate 80 has been involved in the development of severe non-immunological reactions.[2] Indeed, polysorbate 80, an excipient in omalizumab, was thought to be the culprit of anaphylactoid reactions similar to those of our patient in two asthmatic patients after more than a year of successful omalizumab therapy.[3] More recently, urticaria has been reported in one patient treated with different biologic drugs approved to treat severe persistent psoriasis, all containing polysorbate 80.[4] The case we report here is the first case of vaccine adverse reaction due to polysorbate 80 hypersensitivity with mechanisms which remain elusive.

Despite the frequent use of polysorbate 80, severe reactions have rarely been reported in the literature, perhaps because of lack of information about the underlying cause of the reaction in similar cases. The prescribing physician may be unaware of the ubiquitous presence of polysorbate 80 or of its potential biological and pharmacologic activity. Therefore, in cases of unclear hypersensitivity reactions, especially after parenteral administration of drugs, polysorbates should be taken into consideration as causative agents.

Learning points

- Excipients should be considered in the diagnostic investigation of allergic drug reactions.
- Skin prick and intradermal tests may be helpful to identify the culprit of drug hypersensitivity reaction.

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Competing interests None.

Patient consent Obtained.

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