

Evaluation and subsequent safe administration of rabies vaccine to a child presumably allergic to the gelatin content of PCECV Rabavert

Malika Gupta, MD, Sayantani Sindher, MD,
Rushani Saltzman, MD, and Jennifer Heimall, MD

Clinical Implications

- Gelatin can cause IgE-mediated or non-IgE-mediated reactions. It is important to know the components of vaccines and be aware of the potential for reaction(s). Desensitization can be considered for vaccine administration in certain cases.

TO THE EDITOR:

IgE-mediated adverse reactions to vaccines are rare. They are estimated to occur in 0.22/100,000 doses of vaccines and are often noted with the first dose.¹ Vaccine components that may elicit an allergic response include active immunizing antigens, conjugating agents, preservatives, stabilizers, antimicrobial agents, adjuvants, and culture media used in the preparation of the vaccine.¹ The proteins most often implicated in vaccine allergies include egg, gelatin, and yeast.^{1,2} Here, we present a case report of an allergic reaction to purified chick embryo cell rabies vaccine and a review of the literature.

Rabies is a rhabdovirus that is transmitted to humans through the saliva of an infected animal. On the basis of 2012 data from the United States, cats constituted approximately 4.2% of the reported rabid animals.³ Rabies is nearly uniformly fatal in immunologically naïve persons.⁴ According to the recommendations by the Advisory Committee on Immunization Practices, previously unvaccinated patients need a 4-dose vaccine for postexposure prophylaxis for rabies on days 0, 3, 7, and 14 after exposure.⁴

There are 2 commercially available rabies vaccines in the United States: a purified chick embryo cell culture vaccine (PCECV, RabAvert[®], Novartis, Basel, Switzerland; 1.0 mL/dose) and a human diploid cell vaccine (HDCV, Imovax[®] Sanofi Pasteur SA, Paris, France; 1.0 mL/dose). RabAvert[®] contains egg protein (<3 ng), bovine gelatin (12 mg), neomycin (<1 µg), chlortetracycline (<20 ng), amphotericin B (<2 ng), and sodium EDTA (0.3 mg), whereas Imovax[®] contains neomycin (150 µg), human albumin (<100 mg), and phenol red indicator (20 µg).^{4,5}

We report the case of a 7-year-old boy who had an allergic-like reaction to the PCECV form of the rabies vaccine (RabAvert[®]). He was subsequently able to complete his vaccinations using HDCV Imovax[®] using a desensitization protocol.

CASE PRESENTATION

A 7-year-old boy presented to his local emergency department immediately after being bitten by a feral cat. He was given a dose of Rabavert[®] (dose 0) with concurrent administration of rabies immune globulin and started on amoxicillin. At home, within 1 hour of RabAvert[®] administration, he complained of chest

discomfort, nausea, and facial swelling. The symptoms resolved without intervention and he continued his prescribed amoxicillin without incident. A second dose of RabAvert[®] was administered 3 days later. Within 1 hour of receiving the vaccine, he returned to the emergency department with facial swelling, chest discomfort, and abdominal pain. His clinical presentation was most compatible with an acute allergic reaction to RabAvert[®] and he was stabilized with only oral diphenhydramine.

For his third dose of the rabies vaccine, he was brought to our tertiary care center emergency department. Given his history of IgE-mediated-like symptoms with the first 2 rabies vaccine doses, consultation with allergy, infectious disease, and the state department of health was initiated. Continued postexposure prophylaxis was recommended.

His medical history revealed no ancillary atopic problems to date. Specifically, he had no history of atopic dermatitis, asthma, allergic rhinitis, or food or drug allergy. His growth and development were appropriate for his chronological age. He had received all childhood immunizations including measles, mumps, rubella (MMR) and varicella vaccines without adverse reactions. He ate chicken frequently but did not care for egg although he could eat egg without obvious adverse effects. He gave a history of eating gelatin-containing foods such as Jell-O without adversity. His family history was negative for atopic disease.

His remaining doses were administered with the gelatin-free HDCV (Imovax[®]). However, because of the presence of neomycin and possible cross-sensitization to the antigenic component between HDCV and PCECV,⁵ such administration was performed using a desensitization protocol (Table I). He tolerated the procedure without incident.

On follow-up, he had negative skin prick testing to neomycin and Imovax[®], but positive skin prick testing to egg and gelatin (Table II).

A subsequent open food challenge to egg was negative. We postulated that the reaction following RabAvert[®] was likely secondary to his sensitivity to gelatin. We have advised that he receive future vaccines containing gelatin with allergist consultation and observation. The vaccines containing gelatin that the allergist should be cautious about include Tripedia (DTaP), Fluzone (influenza), FluMist (influenza), MMR II (MMR), ProQuad (MMR/varicella), Varivax (varicella), Zostavax (varicella), yellow fever, and oral typhoid capsule.

DISCUSSION AND CONCLUSION

In 1997, the Food and Drug Administration licensed RabAvert[®] vaccine against rabies.⁵ Compared to HDCV, approved in 1980, the new PCECV does not show evidence of serum sickness-like reactions.⁵ From 1997 to 2005, approximately 1.1 million doses of RabAvert[®] were administered. Based on the Vaccine Adverse Event Reporting System, 17 of 20 allergic reactions occurred within the first hour after receiving a dose of RabAvert[®].⁵ Of those, 3 patients had a prior reported history of allergy to egg, penicillin, bee venom, or beef product. One individual was subsequently found to be allergic to both egg white and gelatin based on specific IgE evaluation.⁵

Gelatin has been implicated in both IgE⁻¹ and non-IgE-mediated allergic reactions to vaccines.⁸ The gelatin used in

TABLE I. Graded doses of vaccine Imovax[®] (1.0 mL IM) were administered at 15-minute intervals as follows, per protocol⁶

Dose 1	0.05 mL of 1:100 dilution
Dose 2	0.05 mL of 1:10 dilution
Dose 3	0.05 mL of full strength
Dose 4	0.10 mL of full strength
Dose 5	0.15 mL of full strength
Dose 6	0.20 mL of full strength
Dose 7	0.20 mL of full strength
Dose 8	0.20 mL of full strength

mL, milliliter.

TABLE II. Skin prick test results

Allergen	Results
Egg	5/20 mm
Gelatin*	4/20 mm
Neomycin	0/0 mm
Imovax [®]	0/0 mm

mm, millimeter.

*The percutaneous test was prepared with 1 teaspoon of unflavored Knox[®] gelatin mixed with 30 mL of warm normal saline. The wheal and flare size was measured at 15 minutes.⁷

medical applications is almost exclusively bovine or porcine in origin and is a common ingredient of many foods.⁹ In live attenuated viral vaccines, it is used as a heat-stabilizing agent. RabAvert[®] contains less than 12 mg of gelatin, which is similar to the amount of gelatin present per dose in the MMR and varicella vaccines,¹ both of which were previously administered to our patient without adversity. An equal number of reactions are noted to both types of gelatin and sensitized children tend to cross-react.^{8,9} However, appropriate use of desensitization procedures will minimize the risk of anaphylaxis, and many gelatin allergic patients are able to receive vaccines containing gelatin when medically necessary.

Rabies is a life-threatening condition and an allergy to the commercially available vaccines can pose a challenge in a patient requiring postexposure prophylaxis in a timely manner. Awareness of the potential for IgE-mediated sensitivity to rabies

vaccines and their components is important. This allows the appropriate use of desensitization protocols with the safest vaccine product available, to minimize the risk of anaphylaxis and permit full benefit of the vaccine to prevent disease.

Division of Allergy and Immunology, Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, Pa

No funding was received for this work.

Conflicts of interest: Both R. Saltzman and J. Heimall are attending physicians at The Children's Hospital of Philadelphia. M. Gupta and S. Sindher are both fellows at the same hospital.

Received for publication July 29, 2014; revised September 23, 2014; accepted for publication October 2, 2014.

Available online November 18, 2014.

Corresponding author: Jennifer Heimall, MD, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104-4399.

E-mail: heimallj@email.chop.edu.

2213-2198

© 2014 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2014.10.005>

REFERENCES

1. Chung EH. Vaccine allergies. *Clin Exp Vaccine Res* 2014;3:50-7.
2. Wood RA, Berger M, Dreskin SC, Setse R, Engler RJM, Dekker CL, et al. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. *Pediatrics* 2008;122:e771-7.
3. Dyer JL, Wallace R, Orciari L, Hightower D, Yager P, Blanton JD. Rabies surveillance in the United States during 2012. *J Am Vet Med Assoc* 2013;243:805-15.
4. Centers for Disease Control and Prevention. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep* 2010;59:1-9.
5. Dobardzic A, Izurieta H, Woo EJ, Iskander J, Shadomy S, Rupprecht C, et al. Safety review of the purified chick embryo cell rabies vaccine: data from the Vaccine Adverse Event Reporting System (VAERS), 1997-2005. *Vaccine* 2007;25:4244-51.
6. Adkinson NF, Middleton E. *Middleton's Allergy: Principles & Practice*. Philadelphia, PA: Mosby/Elsevier; 2009.
7. Kelso JM, Jones RT, Yunginger JW. Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gelatin. *J Allergy Clin Immunol* 1993;91:867-72.
8. Moylett EH, Hanson IC. Mechanistic actions of the risks and adverse events associated with vaccine administration. *J Allergy Clin Immunol* 2004;114:1010-20.
9. Sakaguchi M, Nakayama T, Inouye S. Food allergy to gelatin in children with systemic immediate-type reactions, including anaphylaxis, to vaccines. *J Allergy Clin Immunol* 1996;98:1058-61.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.