

Change in gelatin content of vaccines associated with reduction in reports of allergic reactions

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Anaphylactic reactions after administration of measles, mumps, and rubella combined vaccine were first identified as gelatin allergy by Kelso et al.¹ Beginning in 1993, anaphylactic reactions were increasingly reported after administration with gelatin-containing vaccines in Japan.²⁻⁴ IgE antibodies against gelatin were detected most frequently from patients with anaphylactic reactions and less frequently from those with urticarial eruptions.⁴ We analyzed the prior immunization history of acellular pertussis vaccine combined with diphtheria and tetanus toxoids (DTaP) among patients with gelatin allergy and suggested that the gelatin-containing DTaP may have a causal relationship to the development of gelatin allergy.⁴ Among 6 manufacturers of DTaP in Japan, two have never used gelatin in the production vaccine. The remaining 4 manufacturers no longer use gelatin, and since February 1999, all DTaPs used in Japan are free of gelatin.

The current measles vaccine contains human serum albumin, gelatin, or both as a stabilizer. Kitasato has chosen to produce live attenuated vaccines by using gelatin as a stabilizer to avoid the potential risk of pathogenic contamination in human serum albumin. Concern over gelatin allergy, however, led Kitasato to change the gelatin from native bovine gelatin to hydrolyzed modified porcine gelatin (Prionex; Pentapharm Corp) in 1998. Prionex gelatin, porcine skin collagen hydrolyzed in the low pH solution and treated at 145°C for 1 hour, showed lower binding activity to IgE antibodies against gelatin (data not shown). Measles and mumps monovalent vaccines with Prionex were introduced in September 1998.

We analyzed the postmarketing clinical adverse reactions before (June 1994-August 1998) and after the introduction of vaccines with Prionex (September 1998-

Abbreviation used

DTaP: Acellular pertussis vaccine combined with diphtheria and tetanus toxoids

December 1999). The results of the number of reported patients with allergic reactions are shown in Table I. The reporting system of adverse reactions remained the same throughout the study period. A detailed case report was obtained from the physician, and the case was registered with the Ministry of Health and Welfare. The allergic reactions were classified into 3 categories: anaphylaxis, urticaria, and generalized eruption. Anaphylaxis was defined as cases in which the patients demonstrated urticaria or angioedema combined with respiratory symptoms, cardiovascular shock, or both. The second group consisted of those with only urticaria as their reaction. We defined generalized eruption as cases in which the patients had eruptions that were different from urticaria. From June 1994 to August 1998, the total amount of measles vaccine shipped was 1.67 million doses, and 18 cases of anaphylaxis (11 cases per 1 million doses) were reported, including that in our previous report.⁴ The total amount of mumps vaccine shipped was 0.70 million doses, and 17 cases of anaphylaxis (24 cases per 1 million doses) were reported. From September 1998 to December 1999, Prionex has been used as the stabilizer, and 0.47 million doses of measles vaccine and 0.13 million doses of mumps vaccine have been on the market. No anaphylaxis was reported after administration of measles vaccine. One case of anaphylaxis was reported among 0.13 million doses of mumps vaccine (8 cases per 1 million doses). The patient had a previous history of having been immunized with 4 doses of gelatin-containing DTaP. As for rubella vaccine, 9 cases of anaphylaxis were reported among 2.05 million doses of bovine gelatin-containing rubella vaccine (4 cases per 1 million doses). After the introduction of rubella vaccine free of gelatin in July 1999, no anaphylaxis has been reported among 0.33 million doses.

The incidence of reported anaphylactic and other potentially allergic reactions to measles and mumps vaccines appears to have decreased sharply. This coincides with the discontinuation of gelatin-containing DTaP and the change to modified porcine gelatin in live attenuated vaccines. Only one patient with anaphylaxis, demonstrat-

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TABLE I. Incidence of allergic reactions after live attenuated vaccines with different gelatin materials from June 1994 to December 1999

Allergic reactions	Measles vaccine		Mumps vaccine		Rubella vaccine	
	Bovine*	Porcine†	Bovine*	Porcine†	Bovine*	None‡
Anaphylaxis	18 (11)	0 (–)	17 (24)	1 (8)	9 (4)	0 (–)
Urticaria	64 (38)	1 (2)	22 (31)	0 (–)	9 (4)	0 (–)
Eruption	178 (107)	2 (4)	48 (69)	0 (–)	76 (37)	5 (15)
No. of doses shipped (in millions)	1.67	0.47	0.70	0.13	2.05	0.33

Numbers in parentheses reveal the rate of reported reactions per million doses of vaccine shipped. We analyzed the data obtained from June 1994 to December 1999.

*Native bovine gelatin was used at a concentration of 0.2% as a stabilizer until August 1998.

†Hydrolyzed modified porcine gelatin (Prionex) was used at a concentration of 0.2% as stabilizer from September 1999.

‡Neither gelatin nor human serum albumin was used as a stabilizer since July 1999.

ing urticaria with mild wheezing, was reported after administration of mumps vaccine containing Prionex. IgE antibodies against gelatin were borderline, and the stimulation index was 1.92 when lymphocytes were stimulated with native bovine gelatin. We could not examine the comparative tests for native bovine gelatin and modified porcine gelatin in this case. When other IgE antibody-positive sera were used, modified porcine gelatin showed low binding activity less than one tenth of native bovine gelatin. We speculate that the use of modified porcine gelatin decreases the reactivity but that the major reason for the reduction of the cases with gelatin allergy is discontinuation of gelatin-containing DTaP. Infants are no longer being sensitized by DTaP because it no longer contains gelatin.

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