

Short communication

Safety and immunogenicity of gelatin-free varicella vaccine in epidemiological and serological studies in Japan

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Abstract

Following gelatin-containing varicella vaccine (1994–1999: 1,410,000 distributed doses), 28 serious anaphylactic reactions and 139 non-serious allergic reactions were reported, with no serious and only five non-serious reactions following gelatin-free vaccine (1999–2000: 1,300,000 distributed doses). All nine sera available from children with serious reactions tested positive for gelatin-specific IgE, whereas 55 of the 70 available from those with non-serious reactions were positive, with one false positive. There was no correlation between gelatin-specific IgE antibody titers and severity of allergic reaction. Post-immunization anti-varicella antibody titers were comparable for both gelatin-free and gelatin-containing vaccine groups. The new gelatin-free varicella vaccine is thought to be safe, with similar immunogenicity to the earlier gelatin-containing vaccine.

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1. Introduction

Since approval of live varicella vaccine (Oka strain) in 1986 in Japan, the Surveillance System of the Research Foundation for Microbial Diseases of Osaka University has been investigating the effectiveness and safety of the vaccine. From 1994, infants have been given acellular pertussis vaccine combined with diphtheria and tetanus toxoid (DTaP) until 12 months of age, before live vaccines such as measles, rubella, mumps and varicella vaccines. Increasing numbers of anaphylactic/allergic reactions to those vaccines were then reported. Almost all these cases had previously been given three or four doses of DTaP containing gelatin [1]. Removal of gelatin from the live measles vaccine resulted in dramatic decrease in anaphylactic/allergic reactions to this vaccine [1]. Gelatin-associated allergic reactions were also reported for

varicella vaccine [2–4], and gelatin-free live varicella vaccine was introduced in 1999. In this study, we report a comparison of the reporting rates of anaphylactic/allergic reactions with gelatin-containing and gelatin-free varicella vaccines, levels of IgE antibodies to gelatin in those who developed anaphylactic/allergic reactions and a comparison of the immunogenicity and safety of the two vaccines using two kinds of antibody assays.

2. Materials and methods

2.1. Varicella vaccines

Live varicella vaccine (Oka strain) prepared at Kannonji Institute, The Research Foundation for Microbial Diseases of Osaka University, gelatin-containing vaccine (~August 1999) and gelatin-free vaccine (~September 1999) were used. As the stabilizer, the former vaccine contained purified

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Table 1

Breakdown of anaphylactic/allergic reactions following immunization with gelatin-containing and gelatin-free varicella vaccines

Varicella vaccine	Degree of seriousness	Anaphylactic reaction	Generalized urticaria	Dyspnea	Shock-like syndrome	Diarrhea	Swelling at injection site	Total
Gelatin- containing	Serious	28	0	0	0	0	0	28
	Not serious	4	118	9	2	1	5	139
Gelatin-free	Serious	0	0	0	0	0	0	0
	Not serious	1	2	0	1	0	1	5

Approximately 1,410,000 doses of gelatin containing varicella vaccine, and approximately 1,300,000 doses of gelatin-free varicella vaccine, were distributed. Varicella vaccines were used alone in all cases.

sucrose 18.0 mg, native gelatin 0.70 mg, hydrolyzed gelatin 9.00 mg and sodium L-glutamate 0.35 mg per dose, and the latter vaccine contained purified sucrose 25.0 mg and sodium L-glutamate 0.36 mg per dose. The virus titer of both vaccines was $2 \sim \times 10^4$ PFU/dose.

2.2. Post-marketing-surveillance system

Reports of adverse reactions relating to vaccination have been received from physicians in entire Japan by the Post-Marketing Surveillance Center of The Research Foundation for Microbial Diseases of Osaka University, in accordance with the Notification issued by the Japanese Ministry of Health and Welfare. Usually family physicians submitted the reports. Reports of adverse reactions following varicella vaccination were classified according to the Medical Dictionary for Regulatory Activities Terminology (MeDRA) recommended by the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use). Anaphylaxis was defined as an allergic reaction with cardiovascular and/or respiratory symptoms. The immediate reactions such as anaphylaxis and shock-like syndrome appeared within 1 h after vaccination. Cases whose main symptom was anaphylactic/allergic reaction from 1994 to 2003 were collected at the Surveillance Center. It could be determined using the Lot no. if the vaccine was gelatin-containing or gelatin-free in 172 of 189 cases not mild in degree, and these cases were classified according to the Lowest Level Terms (LLT) in MeDRA as shown in Table 1. The type and seriousness of the reactions was determined entirely by the physicians who saw each patient. History of the other vaccinations was not solicited.

2.3. IgE antibody measurement

IgE antibody assays were performed using the method described by Sakaguchi et al. [5]. IgE antibodies to bovine gelatin (Wako Junyaku, Tokyo, Japan) was measured using

the CAP system (Pharmacia, Upsala, Sweden). Positive sera were obtained from patients with anaphylactic reactions, and control sera were obtained from vaccine recipients without any adverse reactions. Inhibition studies were performed, and specific inhibition and parallelism were demonstrated.

2.4. Hospital studies

A total of 379 healthy Japanese individuals with no prior history of varicella infection or varicella vaccination were administered live varicella vaccine at the Pediatric Outpatients Clinic of Showa Hospital (Aichi, Japan) between June 1997 and December 2002. The vaccines used were Lot nos. BVZ*051–VZ021, nine lots of gelatin-containing vaccine for 232 cases (119 males and 113 females), aged 1.1–7.8 years (mean 2.54 years), and nine lots of gelatin-free vaccine for 147 cases (70 males and 77 females), aged 1.0–17.8 years (mean 2.74). Blood samples were collected from each subject just before vaccination and 4–6 weeks after for measurement of varicella antibodies. Antibody titers were determined using two methods, immune adherence hemagglutination (IAHA) [6,7] and glycoprotein-based enzyme-linked immunosorbent assay (gpELISA) [8]. Adverse reactions to the vaccine were checked in all instances by vaccinee parents for 4 weeks after vaccination. The *t*- and χ^2 -test were used for statistical comparisons.

3. Results and discussion

3.1. Anaphylactic/allergic reactions following immunization with gelatin-containing and gelatin-free varicella vaccine

The breakdown of anaphylactic/allergic reactions following immunization with gelatin-containing and gelatin-free varicella vaccine is shown in Table 1. Following administration of gelatin-containing vaccine, there were 28 seri-

Table 2

Gelatin-specific IgE antibodies in sera of patients that developed anaphylactic/allergic reaction following administration of gelatin-containing varicella vaccine

Degree of seriousness	Number of cases	Number of serum samples available	Anti-gelatin IgE		
			Positive	False positive	Negative
Serious	28	9	9	0	0
Not serious	139	70	55	1	14

Table 3
IgE antibody titers and seriousness of allergic reactions

Class of IgE antibody titer to gelatin	Seriousness of allergic reaction		
	Serious	Not serious	Total
6	2	1	3
5	1	2	3
4		15	15
3	4	24	28
2	2	13	15
1		1	1
0		14	14
Total	9	70	79

ous reactions and 139 non-serious reactions, whereas there were no serious reactions and only five non-serious reactions following gelatin-free vaccine. Approximately 1,410,000 doses of gelatin-containing varicella vaccine (1994–1999) and approximately 1,300,000 doses of gelatin-free vaccine (1999–2002) were distributed. The estimated rate of allergic reactions was therefore 11.6/100,000 doses for gelatin-containing vaccine and 0.38/100,000 doses for gelatin-free vaccine.

Gelatin-specific IgE antibody assays were performed where sera was available from those who developed anaphylactic/allergic reactions following immunization with gelatin-containing vaccine. The results are shown in Table 2. All of the nine sera of patients who developed serious symptom were positive for anti-gelatin IgE antibodies. Of the 70 sera

from patients who developed not-serious symptoms, 55 were positive and one was false-positive. Examination of the relationship between the IgE antibody titer and the seriousness of the allergic reaction revealed that severity of allergic reaction did not necessarily correlate with the anti-gelatin IgE titer (Table 3). Removal of gelatin is thought to be an important factor that decreased the reports of adverse events following gelatin-free varicella vaccine, but we do not understand whether other factors were present. About five cases that presented allergic reactions following the gelatin-free vaccine, we do not have data to speculate about the cause.

3.2. Comparison of antibody responses and adverse reactions to gelatin-containing and gelatin-free varicella vaccines

Sera of recipients of nine lots, each of gelatin-containing and gelatin-free vaccine, were tested for antibody response using IAHA test and gpELISA. The results are shown in Table 4. Pre-immunization seropositive cases were excluded from this study. Mean antibody titers for the nine gelatin-containing lots were 4.3–5.5 (log 2) by IAHA test and 2.4–2.5 (log 10) by gpELISA, and seroconversion rates were 88.0–100% by IAHA test and 96.0–100% by gpELISA. For the nine gelatin-free lots, mean antibody titers were 4.7–5.7 (log 2) by IAHA test and 2.3–2.6 (log 10) by gpELISA, and seroconversion rates were 92.3–100% by IAHA test and 96.7–100% by gpELISA. No significant differences in the antibody response to the gelatin-containing lots and

Table 4
Mean post-immunization antibody titers (IAHA, gpELISA) and seroconversion rates for each lot of vaccine

Lot no.	Gelatin	No. of cases	IAHA antibody		gpELISA antibody	
			Mean antibody titer ^a (log 2)	Seroconversion rate (%)	Mean antibody titer ^a (log 10)	Seroconversion rate (%)
BVZ*051	+	22	5.3	100	2.5	100
BVZ*052	+	36	5.3	100	2.4	100
BVZ*053	+	18	5.1	100	2.4	100
VZ-02	+	47	4.3	97.9	2.4	100
VZ-04	+	25	4.7	88.0	2.4	96.0
VZ-05	+	21	4.7	100	2.4	100
VZ-06	+	23	4.8	96.3	2.4	100
VZ-07	+	25	4.8	100	2.5	100
VZ-09	+	15	5.5	100	2.5	100
Total nine lots	+	232	4.9 (S.D. 1.16)	97.4	2.4 (S.D. 0.29)	99.6
VZ-11	—	27	4.8	100	2.3	100
VZ-12	—	11	4.9	100	2.3	100
VZ-13	—	17	4.7	100	2.4	100
VZ-14	—	5	4.8	100	2.5	100
VZ-15	—	19	5.3	100	2.6	100
VZ017	—	13	5.5	100	2.5	100
VZ018	—	12	5.7	100	2.4	100
VZ020	—	30	5.2	96.7	2.4	96.7
VZ021	—	13	4.8	92.3	2.3	100
Total nine lots	—	147	5.1 ^b (S.D. 1.20)	98.6	2.4 ^c (S.D. 0.34)	99.3

^a Post-immunization antibody titer of the seroconverters.

^b $P = 0.09$ vs. gelatin-containing lots (t -test).

^c $P = 0.67$ vs. gelatin-containing lots (t -test).

Table 5
Clinical reactions and days after vaccination

Reaction	Number (%)			
	Gelatin (+)	Gelatin (–)	Gelatin (+)	Gelatin (–)
	Days 0 ^a –2		Days 7–20	
Fever ($\geq 37.5^{\circ}\text{C}$)	17/232 (7.3)	15/147 (10.2)	54/232 (23.3)	31/147 (21.1)
Rash at injection site	63/232 (27.2) ^b	8/147 (5.4) ^b	2/232 (0.9)	1/147 (0.7)
Rash at other site	14/232 (6.0) ^c	2/147 (1.4) ^c	10/232 (4.3)	6/147 (4.1)

^a Day 0 is the day of vaccination.

^b $P \leq 0.01$ from χ^2 -test, for gelatin (+) vs. gelatin (–).

^c $P = 0.03$ from χ^2 -test, for gelatin (+) vs. gelatin (–).

gelatin-free lots were detected with either method. Decrease in local reactions and rash with use of gelatin-free varicella vaccine was observed between days 0 and 2 after vaccination (Table 5). The mean interval between the date of approval by Quality Control at the National Institute for Infectious Diseases and the date of giving of the vaccine to children was 273 days for gelatin-containing vaccine and 239 days for gelatin-free vaccine, with no significant difference between the two groups. These results indicate that gelatin-free varicella vaccine is safe, with comparable immunogenicity to the earlier gelatin-containing varicella vaccine. However, because the sample size was small, further studies with additional samples should be carried out for the above conclusion.

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