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Serologic response and reactogenicity to booster immunization of healthy seropositive adults with live or inactivated varicella vaccine

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Summary

The immunogenicity and reactogenicity of live and heat-inactivated varicella vaccine were evaluated in 95 healthy seropositive adults (mean age, 32 yrs). Live-attenuated vaccine containing 28 000 pfu, 2800 pfu, or 280 pfu of Oka/Merck strain virus (8.4, 0.84, and 0.08 antigen units, respectively) or heat-inactivated vaccine with comparable antigen content (7.1, 0.71, and 0.07 antigen units) was administered subcutaneously to 15 to 16 adults per group in a randomized, single-blind study. ELISA antibody responses were dose-dependent but independent of whether the vaccine was live or inactivated. Mean titers reached a peak on day 14 and remained elevated through day 42 in recipients of the highest dosages but declined by followup at eleven months. A minority of vaccinees developed a four-fold or greater increase in antibody titer on day 14 (25 to 31 percent in the high-dose groups [≥ 7.1 antigen units], ≤ 7 percent of other groups). The vaccine was generally well tolerated. Localized erythema and swelling occurred at the injection site in 44 to 56 percent of the high- and middle dose recipients [≥ 0.71 antigen units], compared with 0 to 6 percent of those receiving the lowest dose. Although statistically significant increases in varicella antibody titer were observed after immunization with high doses of live or inactivated vaccine, the duration and clinical significance of this booster effect remains to be determined.

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Introduction

A live varicella vaccine is currently being developed for prevention of varicella in immunocompromised and healthy children and susceptible healthy adults (Gershon, 1987; Johnson et al., 1988). It has also been postulated that booster immunization(s) of seropositive adults with this vaccine might increase immune responses and prevent episodes of zoster among the elderly (Harnisch, 1984; Burke et al., 1982; Bergen, 1981; Miller, 1980; Gershon, 1987; Arbeter et al., 1986). It is unclear whether such a vaccine would need to contain infectious virus. Furthermore, repeated administration without prior determination of antibody titers might be done, for example, as a booster in adults if routine childhood immunization becomes accepted or in the health care setting to prevent nosocomial infections (Preblud, 1988). Inactivated virus immunization may also be more appropriate for individuals with decreased immune function, who may be at risk for complications from live virus vaccine. In a pilot study to evaluate the immunogenicity and reactogenicity of booster immunization with varicella vaccine, we administered the live or heat-inactivated Oka/Merck strain vaccine at three dose levels to healthy seropositive adults and followed serum antibody responses through six weeks. Durability of response was assessed by measuring antibody titers at 11 months in vaccinees from the highest dose groups.

Materials and Methods

Subjects

One hundred and two healthy adults between the ages of 18 and 49 yrs, who recalled having had varicella, met the initial entry criteria for participation after giving informed consent in accordance with the University of Virginia Human Investigation Committee. Subjects were excluded if they had had zoster within the past year or exposure to varicella within eight weeks prior to vaccination; had an immune deficiency, neoplastic disease or depressed immunity secondary to steroid or immunosuppressive therapy; had been given another vaccination within a month or immune globulin within three months prior to vaccination; had sensitivity to neomycin, or were pregnant or lactating. Participants were advised not to receive any other vaccine or immune globulin within one month of vaccination unless medically necessary. Volunteers were told not to take salicylates during the six weeks after vaccination, and to avoid routine use of nonsteroidal anti-inflammatory agents. Subjects were assigned to one of six vaccine groups based on the order in which they reported to the study site.

Written informed consent was obtained from all participants and the guidelines for human experimentation of the U.S. Department of Health and Human Services and those of the University of Virginia Human Investigation Committee were followed in the conduct of these studies.

Varicella vaccine

Both live and heat-inactivated varicella vaccines were prepared at three dosage levels. A high-potency lot of Oka-strain varicella vaccine (C-M849, Merck, Sharp and Dohme Research Laboratories [MSDRL], West Point, PA) containing 28 000 plaque forming units (pfu) per ml (see below) was reconstituted with sterile distilled water at the University of Virginia. This vaccine which was assayed for varicella antigen content at MSDRL (see below) and estimated to contain 8.4 antigen units per ml, was administered to Group A. It was diluted 1:10 in sucrose-phosphate-glutamate-human albumin solution (SPGA) to yield 2800 pfu and 0.84 antigen units per ml for use in Group B. It was further diluted 1:10 in SPGA to yield 280 pfu and 0.084 antigen units (Group C). All of these live vaccine preparations were kept on ice and used within 2 h of preparation. Heat-inactivated vaccine was prepared by heating at 56°C for 30 min an aliquot of vaccine from the same lot containing 28 000 pfu and 8.4 antigen units per ml. After heating, there was no live virus detected and a slight drop in antigen to 7.1 units per ml. This product was given to Group D. Groups E and F received 1:10 and 1:100 dilutions of the heat-inactivated product in SPGA, containing 0.71 and 0.071 units of antigen per ml, respectively. The heat-inactivated vaccine preparations were kept on ice and used within 4 h of preparation.

Plaque assay

MRC-5 cells grown to 75% confluency in 60-mm plates were inoculated in quintuplicate with 0.1 ml of virus diluted in SPGA, and incubated for 1 h at 35°C. The plates were then fed with maintenance medium containing 2% fetal bovine serum and incubated for 7 days at 35°C in a CO_2 incubator. They were subsequently drained, stained with Coomassie Blue and counted under low magnification. pfu values for the vaccine preparation were calculated from the mean value obtained by assay of 9 vials of vaccine.

Varicella antigen assay

An unpublished 'dot-blot' method (P.M. Keller and P.J. Provost, MSDRL) was used to estimate the varicella virus antigen content of vaccine lot C-M849. Briefly, the vaccine was adsorbed onto nitrocellulose and reacted with human post-zoster serum. The degree of reactivity of antigen was quantitated by comparison to a reference vaccine with an assigned value of 26 antigen units per ml, which had been quantitated in comparison to a purified varicella virus preparation of known protein content.

Study design

Participants were randomly assigned to one of the six vaccine groups and received one 1.0-ml subcutaneous injection of vaccine into the deltoid region. The volunteers and the laboratory technicians performing the serologic studies were unaware of their study group, whereas the evaluating nurses and physicians were not blinded. Sera for antibody titer to varicella-zoster virus were obtained on the day of immunization and post-immunization days 5, 10, 14, 28 and 42. During this 42-day period, participants recorded daily symptoms including sore arm, swelling at injection site, rash, or fever, in addition to a daily oral temperature. Unusual rashes and varicella or zoster-like lesions were examined by a physician. After reviewing the antibody responses through day 42, subjects from groups A, B, D, and E were invited to return for determination of varicella-zoster antibody titers at 11 months (47 weeks). These subjects were asked about the development of zoster and exposure to zoster or varicella since vaccination.

Serologic evaluation

Sera were obtained on all volunteers at baseline, days 5, 10, 14, 28 and 42, and assayed by ELISA technique for antibody to varicella-zoster virus using total VZV antigen at MSDRL (Shehab and Brunell, 1983). The VZV antigen preparation used in the ELISA assay was similar to that contained in the vaccine and was prepared from strain KMcC VZV grown in MRC-5 cells. The infected cell sheets were washed with PBS and harvested in PBS with the aid of glass beads. This material was disrupted by sonication and clarified by low speed centrifugation. Uninfected MRC-5 cell harvests were treated similarly, and this material, adjusted to the same Lowry protein level as the viral preparation, served as the control antigen in the ELISA. Optical density values were converted to titers by comparison to standard curve with sera of known reactivity (Provost et al., 1991). Each subject's samples through day 42 were assayed simultaneously at one dilution. Sera obtained at 11 months were assayed by ELISA in parallel with the participant's day 42 sera, so that direct comparisons between titers at 11 months and day 42 were made on the ELISA values obtained when the samples were assayed simultaneously at the same dilution. For comparison with the baseline titer, the 11-month value was adjusted by the relative difference in results for the two assays of the day 42 sample (measured titer at 11 months $\times$ [day 42 titer by assay 1 $\div$ day 42 titer by assay 2] = adjusted titer at 11 months).

Analysis of data

Because of the wide range of pre- and post-immunization titers, all sera from all subjects could not be assayed at the same dilution. To allow for determination of serologic response for each individual vaccinee, the ELISA

assay on the serum samples from a particular subject through day 42 was performed at a single serum dilution. Changes from baseline titer were examined for each group and analyzed using the least squares means test. Comparisons between day 42 and month 11 titers were done with the paired *t*-test. Data comparing proportions between groups utilized Fisher's exact test. All *P*-values are two-tailed.

Results

Subjects

All of the 102 eligible subjects who were screened had detectable antibody to varicella-zoster virus (titer $\geqslant$ 1:8 by indirect fluorescent antibody, Electro-Nucleonics Inc., Columbia, MD). Ninety-five of these subjects reported for vaccination. The mean ages (A-34 yrs, B-32 yrs, C-33 yrs, D-32 yrs, E-32 yrs, F-29 yrs) and gender distribution (percent female; A-56%, B-94%, C-63%, D-81%, E-93%, F-75%) were similar for recipients of corresponding live and heat-inactivated vaccine except that members of group F were younger than group C ($P=0.02$). Of the 63 subjects from groups A, B, D, and E invited for follow-up testing at 11 months, sera were obtained from 56 (16 A, 13 B, 13 D, and 14 E).

Clinical reactions

Local reactions occurred with the same frequency in recipients of the live and heat-inactivated vaccines. During the first 72 h after vaccination, 33 percent of recipients of the live vaccine compared with 30 percent of recipients of the heat-inactivated vaccine reported pain, swelling, or redness at the injection site (Table 1). These local reactions were more frequent in the higher dose than low

TABLE 1

Injection site reactions during 72 h after immunization with live and inactivated OKA/Merck varicella vaccine in seropositive adults

Group (*n*)	Vaccine type	Antigen units	pfu	Total local reactions	Percent of subjects		
					Erythema	Induration	Soreness
A (16)	L	8.4	28 000	56[a]	38[b]	44[a,c]	50[a]
B (16)	L	0.84	2 800	44[a]	13	6	31[b]
C (16)	L	0.084	280	0	0	0	0
D (16)	I	7.1	0	38[d]	19	6[c]	31
E (15)	I	0.71	0	47[e]	20	13	40[e]
F (16)	I	0.071	0	6	6	0	6

L = live; I = heat-inactivated at 56°C for 30 min.
[a] $P<0.01$ vs group C. [b] $0.01<P<0.05$ vs group C. [c] $P=0.04$ group A vs group D. [d] $0.05<P<0.1$ vs group F. [e] $0.01<P<0.05$ vs group F.

TABLE 2

Systemic complaints and febrile reactions after immunization with live or inactivated OKA/Merck varicella vaccine in seropositive adults

Group (*n*)	Vaccine type	Antigen units	pfu	Percent of subjects (days 0–42 post-immunization)							
				Temperature		Head-ache	Ma-laise	Nau-sea	Fati-gue	Arthral-gias	Myal-gias
				⩾ 37.8°C	⩾ 38.3°C						
A (16)	L	8.4	28 000	6	0	38	13	25	19	6	19
B (16)	L	0.84	2 800	12	6	31	6	19	19	0	19
C (16)	L	0.084	280	31	12	38	6	13	6	0	6
D (16)	I	7.1	0	19	0	50	6	19	25	6	6
E (15)	I	0.71	0	40	7	53	13	20	67	13	27
F (16)	I	0.071	0	32	13	38	0	25	25	6	19

L = live; I = heat-inactivated at 56°C for 30 min.

dose groups ($P < 0.001$ for A + D vs C + F and $P < 0.001$ for B + E vs C + F). None of these complaints was sufficiently severe to warrant medical attention.

Over the 6-week observation period, febrile reactions (oral temperature ⩾ 38.3°C) were reported infrequently. Only one vaccinee (Group C) had a temperature ⩾38.3°C during the six days following vaccination. Non-specific systemic complaints were common in all groups and were not related to vaccine dose (Table 2). One vaccinee (Group A) sought medical attention for symptoms of myalgias, nausea, and lightheadedness which began within 24 h after vaccination and resolved in 3 days.

None of the subjects developed a varicella-related rash or zoster over the six week observation period. No subject reported the occurrence of varicella or zoster in a family contact during the study period. During the 11-month follow-up period, six vaccine recipients had known exposures to varicella or zoster (3 B, 1 D, 2 E). No vaccinee developed zoster or varicella.

Serologic response

Antibody responses through day 42 were related to the antigen dose but were independent of whether the vaccine was live or heat-inactivated (Fig. 1). Peak antibody responses generally occurred by day 14. The ratio of ELISA antibody titer on day 14 to pre-immunization titer (mean ± SD) was 3.1 ± 1.9 and 3.8 ± 4.0 for groups A and D, respectively ($P < 0.0001$ vs baseline), 1.9 ± 1.1 for group B ($P = 0.09$), 2.5 ± 1.5 for group E ($P = 0.005$), and 1.5 ± 0.6 and 1.2 ± 0.5 for groups C and F, respectively. Antibody titer ratios (day 42 ÷ baseline) remained significantly elevated at 42 days in groups A (2.9 ± 1.9) and D (3.0 ± 2.9) ($P < 0.0001$ vs baseline) and E (1.9 ± 0.9, $P = 0.03$), but not in groups C (1.4 ± 0.5), F (1.3 ± 0.3), or B (1.5 ± 0.7). A minority of vaccinees demonstrated a four-fold or greater increase in serologic titer (Table 3).

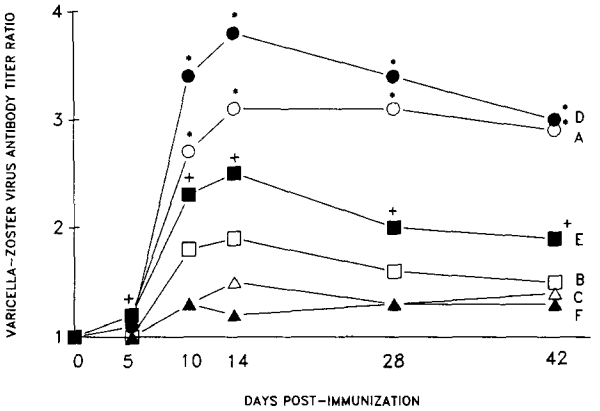

Fig. 1. Mean-fold increase in varicella-zoster antibody titer (ELISA antibody titer/pre-immunization titer) by day after immunization of healthy seropositive adults with live (A, B, C, open symbols) or heat-inactivated (D, E, F, closed symbols) varicella vaccine. Vaccine was administered at three dose levels (antigen content; groups A and D, 8.4 and 7.1 antigen units; B and E, 0.84 and 0.71 units; C and F, 0.08 and 0.07 units). +, = $P < 0.05$ vs day 0 pre-immunization titer; *, = $P < 0.001$ vs day 0 pre-immunization titer.

Mean antibody titers at 11 months were lower for each group than at day 42. The ratios of titers (mean ± SD) at 11 months to day 42 were 0.6±0.3, 0.8±0.2, 0.7±0.3, and 0.7±0.2 for groups A, B, D, and F respectively ($P < 0.05$, for each group, day 42 vs month 11). These ratios did not differ between the groups. Correspondingly, the titer at 11 months did not differ significantly from the baseline titers for groups A (ratio of month 11 titer to baseline, 1.5±1.1, $P = 0.08$ vs baseline), D (1.8±1.6, $P = 0.10$), B (1.0±0.4) or E (1.3±0.8). Of the five subjects who had four-fold or greater rises in antibody

TABLE 3

Proportion of healthy seropositive adults having 4-fold or greater VZV antibody rises from baseline by ELISA following immunization with live or heat-inactivated OKA/Merck varicella vaccine

Group (*n*)	Vaccine type	Antigen units	pfu	No. (%) of subjects on post-immunization		
				Day 14	Day 42	Month 11[a]
A (16)	L	8.4	28 000	5 (31)	3 (19)	1
B (16)	L	0.84	2 800	1 (6)	0 (0)	0
C (16)	L	0.084	280	0 (0)	0 (0)	–
D (16)	I	7.1	0	4 (25)	3 (19)	2
E (15)	I	0.71	0	1 (7)	0 (0)	0
F (16)	I	0.071	0	0 (0)	0 (0)	–

L = live; I = heat-inactivated at 56°C for 30 min.

[a]Not all subjects were tested at 11 months. Vaccinees from groups A, B, D and E were invited to return at 11 months. Data shown include results from five of the six high-dose recipients (groups A and D) who had 4-fold or greater antibody titer rise at day 42.

titer on day 42 and who were retested at 11 months, four-fold or greater increases were sustained in three (one from group A, two from group D).

Discussion

This study is the first to evaluate the immunogenicity of both the live and heat-inactivated Oka/Merck varicella vaccine in healthy seropositive adults. In young and middle-aged adults immunized subcutaneously with booster doses of up to 28 000 pfu ($\geqslant$7.1 antigen units), we found statistically significant, dose-dependent rises in serum antibody titers that were independent of whether the vaccine was live or heat-inactivated. A minority of vaccinees, however, demonstrated four-fold or greater rises in ELISA antibody titers. On day 14, only 31 percent of the recipients of the live 28 000 pfu vaccine (8.4 antigen units) and 25 percent of the group receiving the comparable inactivated vaccine (7.1 antigen units) had a four-fold or greater rise in antibody titers. This occurred despite the fact that vaccinees in these groups received considerably higher virus inoculum and/or antigen content than have been administered in earlier trials (Bergen et al., 1990).

Our results and the limited available data on immunization of seropositive individuals suggest that greater quantities of antigen are needed to boost antibody titers than to produce a primary response. In prior studies, most seropositive vaccinees did not recall a history of varicella and were immunized as part of studies of presumably seronegative individuals. Ten of 22 seropositive children given a dose of 8700 pfu of the Oka/Merck vaccine developed a four-fold or higher rise in titer (Weibel et al., 1984). However, Arbeter et al. (1986) reported that 23 of 24 seropositive children given one of three different varicella vaccines had an antibody boost of four-fold or greater at six to eight weeks. Among 11 seropositive adolescents and adults through 40 yrs of age who received 4350 pfu, and four who received 870 pfu, a four-fold or greater boost in antibody titer at two to three weeks or six to eight weeks was seen in 47 percent (Arbeter et al., 1986). In another study of older seropositive adults aged 51 through 86 yrs who were followed for four months after a 3500 pfu booster with the live Oka-strain vaccine, only two of 25 (8 percent) had a four-fold or greater rise in antibody titer (Starr et al., 1987), a finding confirmed by our low frequency of response (1 of 16, 6%) in the 2800-pfu group. In neither study of seropositive adults were long-term serologic responses reported.

Our study did not include measures of VZV-specific cell-mediated immunity, and it is likely that a higher proportion of healthy recipients of the live virus vaccine would develop an immunologic response than would be indicated by measurement of antibody titer rises alone. Starr and colleagues (1987) observed that a higher percent of seropositive older adult vaccinees had lymphocytic proliferation responses than four-fold or greater rises in antibody titer. VZV-specific lymphocyte proliferation significantly increased post-immunization in

85 percent of those aged 50 through 59 years old but in only 20 percent of those greater than 70 years of age (Starr et al., 1987). In the study by Arbeter et al., 66 percent of adult vaccinees had a boost in cellular immunity and/or antibody titers compared with an increase in antibody titer alone in 47 percent (Arbeter et al., 1986). The cell-mediated responses to the inactivated vaccine are undefined in seropositive adults.

Prior studies of the varicella vaccine have focused on immunization with live virus. An important finding in our study was that the antibody responses in recipients of the heat-inactivated vaccine were similar to those in recipients of live vaccine. This suggests that virus replication was not necessary for the humoral immune responses we observed. The similar dose response in the live and inactivated vaccine recipients is also consistent with the recent findings of Bergen et al. (1990) in seronegative children that the total antigen content may affect the immune response to the live VZV vaccine. If stimulation of cell-mediated immunity could also be demonstrated, these findings would favor the use of an inactivated vaccine in certain clinical situations. The risk of vaccine virus infection resulting from use of the live virus vaccine would be eliminated in those with severely impaired immunity. Persons with impaired cellular immunity or prior to an anticipated decrease in cellular immunity, such as those recently infected with HIV or oncology patients prior to chemotherapy, might be safely boosted with such a vaccine.

We found that the vaccine was generally well tolerated. No zosteriform or vesicular rashes, indicative of viral replication, were noted. Local reactions such as swelling, pain, or erythema during the first 72 h post-vaccination occurred in a dose-dependent manner and were independent of whether the vaccine was live or heat-inactivated. Such local reactions were noted by approximately one-half of the high and middle dose ($\geqslant$ 2800 pfu; $\geqslant$ 0.71 antigen units) recipients. This is in accord with the observations of Arbeter and colleagues who observed local reactions in 47 percent of 15 seropositive adult recipients of 870 pfu or 4350 pfu, but is higher than the 21 percent frequency they reported in seronegative adults (Arbeter et al., 1986) and the 10 percent frequency in seronegative children (Gershon, 1987) and adults after one dose of vaccine reported by Gershon and colleagues (Gershon et al., 1988). The pathophysiologic mechanisms involved in the local reactions are not defined; our results suggest that as was observed in the specific antibody response, viral replication is not critical but that antigen dose is an important variable.

Studies are needed to ascertain the magnitude and durability of VZV-specific cellular immune responses to high dose booster immunization with live or inactivated vaccine in older adults and immunocompromised seropositive patients. If such investigations show that the response to inactivated vaccine is similar in magnitude and duration to live vaccine, long-term trials with an inactivated vaccine would be warranted to determine possible efficacy in reducing the incidence or severity of herpes zoster in such persons.

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