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Immunization of Elderly People with Two Doses of Influenza Vaccine

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A total of 104 elderly patients were immunized with one or two doses of the commercial 1985–1986 inactivated influenza vaccine formulation. Two types of vaccines (split virus [SV] vaccine and whole virus [WV] vaccine) and one or two doses 1 month apart were given. No difference in local or systemic reactions was noted among the four groups. The reciprocal geometric mean hemagglutination inhibition antibody titers against influenza A/Philippines/82 (H3N2) after one or two doses were: 78 for SV vaccine (one dose), 65 for SV vaccine (two doses), 55 for WV vaccine (one dose), and 51 for WV vaccine (two doses). Similar nonsignificant differences were observed for the other two antigens contained in the vaccine. The percentage with a hemagglutination inhibition titer of ≥1:40 also did not differ after one or two doses. We then compared the postvaccination hemagglutination inhibition titers in young and old patients from previous studies in which apparent differences had appeared. We retested all sera simultaneously on the same day with the same reagents. No significant differences were apparent among age groups. In summary, the humoral immune response to inactivated influenza vaccine in healthy ambulatory elderly patients who have been previously immunized may not differ significantly from that of children and young adults. A booster dose 1 month after the first dose does not enhance immune responses in the elderly.

The equality of the immune response to influenza vaccine in young and old adults is still a subject of debate. Several studies indicate significant differences in responses (5, 6, 10). Others show no difference (1, 12). The discrepancy among these findings may be caused by differences in the health status of the elderly adults, or there may be a subgroup of the elderly who respond poorly to immunization although the rest respond in a satisfactory way (13).

We have been studying different methods for improving the immune responses to influenza vaccine. First, we administered two to three times the standard vaccine dose. Although the higher doses were well tolerated, the immune response improved only slightly (P. A. Gross, M. E. Weksler, and G. V. Quinnan, Jr., Program Abstr. 25th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 972, 1985). Higher multiples of the standard dose will undoubtedly be necessary to significantly improve the immune response (9, 12). The cost of higher doses may be prohibitive. Alternative approaches need to be examined.

In the present study, we studied whether two standard doses given 1 month apart would enhance the immune response of elderly adults. We reasoned that the second dose might significantly boost the antibody response that was stimulated by the initial dose. In young children, two doses are clearly superior to one dose (8, 14).

MATERIALS AND METHODS

In the fall of 1985, we immunized 104 elderly persons with standard doses of the commercially licensed influenza vaccine (4). The vaccines contained 15 μg of hemagglutinin of each of influenza A/Philippines/82 (H3N2), influenza A/Chile/83 (H1N1), and influenza B/USSR/83. Both split virus (SV) and whole virus (WV) vaccine preparations were used. The volume of each dose was 0.5 ml. The SV vaccine was manufactured by Parke, Davis & Co., Detroit, Mich., and the WV vaccine was made by Squibb/Connaught Laboratories, Inc., Swiftwater, Pa.

The vaccinees were healthy ambulatory patients above 65 years of age who attended the geriatric clinic at Cornell University Medical College, New York, N.Y. Most had been immunized in the previous year.

The patients were randomly assigned to one of four groups. Group A received one dose of SV vaccine; group B received two doses of SV vaccine given 1 month apart; group C received one dose of WV vaccine; and group D received two doses of WV vaccine given 1 month apart.

We also compared the immune response in this elderly group with that in a younger group of children and young adults with cystic fibrosis. The younger patients are immunized annually as part of an influenza vaccine study at St. Vincent's Hospital in New York City described previously (9). The younger patients received one dose of 0.5 ml of the SV vaccine.

Serum hemagglutination inhibition (HI) antibody titers were determined before immunization and 4 weeks after the first and second immunizations by methods described previously (9, 11). Serologic titers are expressed as the reciprocal of the highest serum dilution causing HI. Statistical analysis was done by using the chi-square test to compare proportions. Fisher's exact test was used instead of the chi-square test when any number in the proportion was less than five. Student's *t* test was used to compare geometric mean HI titers. Two-tailed testing was used for citing of *P* values.

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TABLE 1. HI antibody responses after influenza immunization of elderly patients

Group	Vaccine type	No. of doses	No. of subjects	Reciprocal geometric mean antibody titers to:								
				A/Philippines/82 (H3N2)			A/Chile/83 (H1N1)			B/USSR/100/83		
				Before immunization	After 1 dose	After 2 doses	Before immunization	After 1 dose	After 2 doses	Before immunization	After 1 dose	After 2 doses
A	SV	1	27	20	78	NA[a]	56	99	NA	60	114	NA
B	SV	2	29	23	65	70	85	120	97	39	65	60
C	WV	1	27	17	55	NA	42	112	NA	25	58	NA
D	WV	2	21	25	51	49	56	99	99	51	71	74

[a] NA, Not applicable.

TABLE 2. HI antibody level percentages after influenza immunization of elderly patients

Group	Vaccine type	No. of doses	No. of subjects	% with HI titer ≥1:40 with:								
				A/Philippines/82 (H3N2)			A/Chile/83 (H1N1)			B/USSR/100/83		
				Before immunization	After 1 dose	After 2 doses	Before immunization	After 1 dose	After 2 doses	Before immunization	After 1 dose	After 2 doses
A	SV	1	27	37	89	NA[a]	70	89	NA	85	93	NA
B	SV	2	29	38	79	86	72	83	83	59	86	79
C	WV	1	27	26	74	NA	67	100	NA	41	81	NA
D	WV	2	21	48	71	67	67	86	86	76	86	90

[a] NA, Not applicable.

RESULTS

Patients were randomly assigned to one of four groups. They received either one or two doses of either SV or WV vaccine (Table 1).

There were 21 to 29 patients in each group. The mean ages were between 72 and 74 years. The percentages previously vaccinated were 71 to 92%.

The geometric mean HI antibody titer after two doses did not significantly increase over that observed after one dose. In fact, the titer was stationary after the second dose (Table 1).

With the influenza B/USSR/83 strain, the geometric mean HI titer after one dose of SV vaccine was higher than that seen after two doses (1:114 versus 1:60). Although this difference is significant, the difference in prevaccination titers probably accounts for the difference in postvaccination titers. The prevaccination titer was higher in the group that exhibited the higher postvaccination titer.

The percentage of subjects with an HI titer equal to or greater than 1:40 is shown for the same serum pairs in Table 2. The titer of 1:40 was selected because this is the level of HI antibody that usually protects one from acquiring influenza virus infection (9). Between 70 and 100% of patients developed presumably protective antibody titers against all three vaccine strains. No significant differences were observed among the four vaccine groups. A second dose did not improve the antibody titer that developed after one dose.

Sera from groups of young patients (mean age, 14 years) and old patients (mean age, 73 years) were compared for geometric mean HI antibody titers and the percentage with HI titer equal to or greater than 1:40 (Table 3). Against all three vaccine strains, no significant differences appeared when we compared the antibody titers in the young and old.

DISCUSSION

Two doses of influenza vaccine did not improve the HI antibody response in the elderly persons we studied. Previous studies by Brandriss et al. (2) and Cate et al. (3) also did not show any improvement in the humoral immune response when a second dose was added. Several reasons may account for why two doses were not superior to one dose. First, the elderly patients vaccinated were healthy ambulatory individuals. The impaired immune response that might be overcome with a vaccine booster may be more likely in infirm or bedridden elderly persons or in a small subgroup of healthy elderly persons (6, 13). Second, the elderly patients studied had been previously immunized either the previous year or the year before that. Consequently, the first immunizing dose may have maximally stimulated their HI antibody titers. Prior immunization may have adequately primed the ability of their humoral immune system to respond to the influenza vaccine strains. Last, the group sizes may have been insufficient to detect a small but significant difference. Although such an error related to sample size is possible, the differences observed were so small that it is unlikely that the

TABLE 3. Comparison of HI antibody responses to influenza vaccine in ambulatory elderly patients and children and young adults with cystic fibrosis

Age group	No. of subjects	Geometric mean HI titer[a] (% with HI titer ≥1:40)					
		A/Philippines/82 (H3N2)		A/Chile/83 (H1N1)		B/USSR/100/83	
		Before immunization	After 1 dose	Before immunization	After 1 dose	Before immunization	After 1 dose
Young	45	19 (42)	36 (67)	28 (51)	48 (80)	33 (56)	90 (82)
Old	25	18 (22)	50 (52)	21 (25)	62 (70)	24 (36)	59 (72)

[a] Reciprocal HI titers with each test antigen.

use of larger study groups would have revealed a significant difference and that such a difference would have clinical relevance (7).

It appears from this and other studies (1; Gross et al., 25th ICAAC) that the previously immunized healthy elderly person is likely to develop an adequate antibody response to influenza vaccine. The response is unlikely to be inferior to that of younger adults. Further attempts to improve the antibody titers after immunization are probably not necessary for the healthy ambulatory elderly person who is immunized regularly.

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