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Time to Earliest Peak Serum Antibody Response to Influenza Vaccine in the Elderly

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The earliest time at which serum antibody levels peak following administration of an influenza virus vaccine in elderly persons is not clearly defined. We compared the time intervals of 1 and 2 weeks after vaccination. A commercial trivalent vaccine containing the hemagglutinins of influenza viruses A/Texas/36/91 (H1N1), A/Johannesburg/33/94 (H3N2), and B/Harbin/7/94 was used. The hemagglutination inhibition (HAI) antibody titers at 1 week after vaccination were significantly lower than the HAI titers at 2 weeks postvaccination for all three vaccine components.

Knowing the time to the appearance of the peak hemagglutination inhibition (HAI) antibody response to an influenza virus vaccine is important for experimental and practical purposes. During an influenza epidemic, this information can help to guide decisions on how long antiviral drugs, such as amantadine and rimantadine, have to be given after vaccination before optimal levels of HAI antibody appear and drug administration can be stopped. When new vaccine strains are being tested, it will shorten the length of time needed for conducting vaccine trials.

In the first two parts of this series, we compared the peak HAI antibody response at 2, 4, and 6 weeks after vaccination and found the responses to be comparable (7, 9). In the current study, we examined elderly patients at 1 and 2 weeks after influenza virus vaccination to determine whether their peak antibody titers occurred earlier than 2 weeks postvaccination.

After they had given informed consent, elderly patients above 65 years were enrolled at two sites in New York City: the geriatric clinics at Cornell Medical School and the Amsterdam Nursing Home.

Patients received the commercially available 1995-to-1996 trivalent influenza virus vaccine manufactured by Parke-Davis, Morris Plains, N.J. The vaccine contained the hemagglutinins of influenza viruses A/Texas/36/91 (H1N1), A/Johannesburg/33/94 (H3N2), and B/Harbin/7/94. The vaccine was given as a 0.5-ml dose by injection into the deltoid muscle. It was administered from mid-October through mid-November 1995.

Three blood specimens were obtained; the first was drawn at the time of vaccination, and the others were obtained at 1 and 2 weeks postvaccination. Serum HAI antibody titers were determined in microtiter plates as previously described (6). All blood specimens from both study sites were tested simultaneously for each vaccine strain so that comparison of the 1- and 2-weeks-postvaccination values and the intersite comparisons would be valid. The specimens were tested in the Diagnostic Virology Laboratory, Hackensack University Medical Center, Hackensack, N.J. Influenza virus A/Taiwan/1/86 (H1N1) was used for serologic studies instead of influenza virus A/Texas/36/91 (H1N1) as suggested by the Influenza Virus Section, Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Ga. In addition, influenza virus B/Harbin/7/94 is considered to be like influenza virus B/Beijing/184/93. No influenza virus was detected in the geographic area at the time of the study.

Statistical analyses were performed with the Systat, Inc., software program. Group means were compared by using Student's *t* test. Dichotomous variables were compared by using the chi-square test. When one of the cell entries was less than 5, Fisher's exact test was used.

We studied 81 healthy elderly patients from the New York Hospital-Cornell Medical Center geriatric clinics. The mean age for the healthy group was 76 years; 59% were males, and 100% were previously vaccinated. We also studied 32 infirm elderly patients from the Amsterdam Nursing Home. The mean age for the infirm group was 80 years; 55% were males, and 100% had been vaccinated previously.

The postimmunization HAI titers at 1 and 2 weeks following vaccination were different (Table 1). For the influenza virus A/Johannesburg strain, the 2-week geometric mean HAI titer (GMT) was significantly higher than the 1-week GMT for both the healthy and infirm elderly patients (17 versus 26, $P < 0.05$; 32 versus 69, $P < 0.01$). For influenza viruses A/Taiwan and B/Harbin, the infirm elderly again had a significantly higher GMT response at 2 weeks postvaccination than at 1 week (42 versus 73, $P < 0.01$; 34 versus 57, $P < 0.05$). For the other comparisons, the trends were in a similar direction. When we examined the percentage of patients with serum HAI titers equal to or greater than 1:40, the 2-week titers were higher than the 1-week titers for all these strains in the infirm group and for one strain, A/Johannesburg, in the group of healthy elderly patients (33 versus 54, $P < 0.05$). An HAI titer of 1:40 or higher is normally considered protective (3, 4). Some, but not all, of the members of the groups had significant increases in HAI titers between the prevaccination sampling point and 1 week postvaccination. These significant comparisons are not noted in the table.

Several other observations are worthy of comment. While for two of the three strains the preimmunization titers were lower in the infirm group than in the healthy elderly group, the titers were higher in the infirm group postimmunization for all three strains. Hence, in this study, the infirm group did not do

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TABLE 1. Reciprocal serum HAI antibody responses at 1 and 2 weeks after vaccination in healthy and infirm elderly patients immunized with the 1995–1996 trivalent influenza virus vaccine[a]

Influenza virus strain and patient group vaccinated	GMT at:			% of patients with HAI titers of ≥40 at:		
	Prevaccination	1 week after vaccination	2 weeks after vaccination	Prevaccination	1 week after vaccination	2 weeks after vaccination
A/Taiwan/1/86 (H1N1)						
Healthy elderly patients	39	51	58	59	71	72
Infirm elderly patients	26	42[b]	73[b]	49	69	84
A/Johannesburg/33/94/H3N2)						
Healthy elderly patients	12	17[c]	26[c]	20	33[c]	54[c]
Infirm elderly patients	17	32[b]	69[b]	32	56	81
B/Harbin/7/94						
Healthy elderly patients	25	43	54	46	65	67
Infirm elderly patients	19	34[c]	57[c]	27	46	72

[a] $n = 81$ for the group consisting of healthy elderly patients (59% males; mean age, 76 years; 100% previously vaccinated); $n = 32$ for the group composed of infirm elderly patients (55% males; mean age, 80 years; 100% previously vaccinated).
[b] The 2-week value is significantly different from the corresponding 1-week value ($P < 0.01$).
[c] The 2-week value is significantly different from the corresponding 1-week value ($P < 0.05$).

worse than the healthy elderly group, as had been reported in other studies.

The current study, along with our previous studies, documents that the period of peak HAI titers to an influenza virus vaccine extends from 2 to 6 weeks in the elderly. Whether it extends beyond 6 weeks cannot be stated from this study (8); however; this study illustrates that the peak does not occur earlier than 2 weeks postvaccination. Cox and colleagues have done studies showing that the peak serum antibody response occurs at 2 weeks postvaccination for young and middle-aged adults primed to the vaccine subtype (2). The mean ages of their groups were 25, 32, and 41 years. Cox et al. also observed that while many adults achieved a protective titer at 1 week postvaccination, the peak occurred at 2 weeks.

The fact that the peak HAI antibody response for the group appears at 2 weeks and not earlier lends support to the recommendation that amantadine and rimantadine treatment be continued for 2 weeks when these antiviral drugs are given to protect a person from influenza virus A infection before the peak antibody response to the vaccine develops (1).

When information on responses to vaccines is needed rapidly in the elderly, the postvaccination titer should not be drawn prior to 2 weeks after vaccine administration. This statement is expected to be valid when vaccinees are already primed for the vaccine or a related strain (i.e., antigenic drift) by a previous natural exposure or prior vaccination. Whether it applies to unprimed persons when they are first vaccinated with a strain that represents an antigenic shift cannot be stated from this study. In the latter case, our findings might be expected to apply only after a second vaccine dose, containing the shifted strain, is given (5).

In conclusion, this study of 113 patients suggests that peak HAI antibody titers in elderly primed persons first occur at 2 weeks after influenza virus vaccination and not earlier.

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