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

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The earliest time at which serum antibody peaks following administration of influenza virus vaccine in elderly persons is not clearly defined. We compared the time intervals of 2 and 4 weeks after vaccination. A commercial trivalent vaccine containing the hemagglutinins of influenza viruses A/Texas/36/91(H1N1), A/Shangdong/9/93(H3N2), and B/Panama/45/90 was used. The hemagglutination inhibition antibody titers at 2 weeks after vaccination were identical to the hemagglutination inhibition antibody titers at 4 weeks for all three vaccine components.

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

In the first article of this series, we compared the peak HAI antibody response at 4 and 6 weeks after vaccination and found the responses comparable (8). In the present study, we examined elderly patients at 2- and 4-week intervals after influenza virus vaccination to determine whether the peak antibody titer occurred earlier than 4 weeks.

Following their informed consent, elderly patients above 65 years of age were enrolled at two sites in New York City: the Geriatric Clinics at Cornell Medical School and the Amsterdam Nursing Home.

Patients received the 1994-to-1995 commercially available 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/Shangdong/9/93(H3N2), and B/Panama/45/90. The vaccine was given as a dose of 0.5 ml by injection into the deltoid muscle. It was administered from mid-October through mid-November 1994.

Three blood specimens were obtained—the first at the time of vaccination and the others at 2 and 4 weeks after vaccination. 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 values at the 2- and 4-week intervals and the intersite comparisons would be valid. The specimens were tested in the Diagnostic Virology Laboratory, Hackensack University Medical Center, Hackensack, N.J. 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 79 healthy elderly patients from the New York Hospital-Cornell Medical Center geriatrics clinics. The mean age for the healthy group was 75 years; 56% were males, and 44% were previously vaccinated. We also studied 19 infirm elderly patients from the Amsterdam Nursing Home. The mean age for the infirm group was 82 years; 32% were males, and 68% had been vaccinated previously.

The postimmunization HAI antibody titers were equal at 2 and 4 weeks following vaccination (Table 1). Our findings confirm those of an earlier study by Clements and Murphy with 23 healthy young adults between 18 and 35 years old who were seronegative and who lacked a history of prior influenza vaccination (2).

Several other observations are worth comment. The pre- and postimmunization HAI antibody titers were significantly greater in the healthy elderly than in the infirm elderly for both influenza A/Texas and B/Panama. Fewer than 60% of the infirm elderly had HAI antibody titers of 40 or greater against those two vaccine strains. An HAI antibody titer of 40 or greater is normally considered protective (3, 4).

Against the A/Shangdong strain, fewer than 60% of either healthy or infirm elderly subjects had protective titers. In addition, no appreciable differences were noted in the antibody responses of the healthy and infirm elderly for this strain. The clinical significance of this observation with the influenza A(H3N2) strain is unclear, as the finding is not consistently present from other studies (5, 6).

Comparison of the percent of patients with HAI antibody titers of ≥40 before and after vaccination showed significant rises in the healthy elderly for all three strains and in the infirm for influenza B/Panama only.

The sample of patients studied was large enough to minimize a type II error in the healthy elderly group (8).

The present study along with our previous study (8) documents that the period of peak HAI antibody titers to influenza virus vaccine extends from 2 to 6 weeks. Whether it appears earlier than 2 or later than 6 weeks cannot be stated from this study (7).

The fact that the peak HAI antibody response for the group...
appears at 2 weeks lends support to the recommendation that amantadine and rimantadine can be discontinued after 2 weeks when the antiviral drugs are given to protect a person from influenza type A virus infection before antibody to the vaccine develops (1).

When vaccine response information is needed rapidly for the elderly population studied, our observation that HAI antibody peaks at 2 weeks may also be used to speed influenza vaccine trials, as the postvaccination titer could be drawn at 2 weeks rather than at 4 or 6 weeks after vaccination. This statement would be expected to be valid when vaccinees are already primed for the vaccine or a related strain (i.e., antigenic drift) by previous natural exposure or prior vaccination. Whether it would apply 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, it might only be expected to apply after the second vaccine dose with the shifted strain (5).

In conclusion, this study of 98 patients suggests that peak HAI antibody titers occur in elderly persons as early as 2 weeks after influenza virus vaccination.

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REFERENCES

| Influenza virus strain and elderly patient group | Geometric mean titer | % with HAI titer of ≥40 |  |
|-----------------------------------------------|----------------------|------------------------|  |
| A/Texas/36/91(H1N1)                           |                      |                        |  |
| Healthy                                      | 47***                | 82***                  | 58*       |
| Infirm                                       | 17***                | 32***                  | 26*       |
| A/Shangdong/9/93(H3N2)                        |                      |                        |  |
| Healthy                                      | 14                   | 30                     | 24        |
| Infirm                                       | 14                   | 32                     | 28        |
| B/Panama/45/90                               |                      |                        |  |
| Healthy                                      | 33*                  | 57***                  | 55**      |
| Infirm                                       | 19*                  | 28***                  | 21**      |

| Characteristics for patient groups: 79 healthy elderly patients; 56% males; mean age, 75 years; 94% previously vaccinated. 19 infirm elderly patients; 32% males; mean age, 82 years; 84% previously vaccinated.  |

| Tests of significance: *, P = 0.02; **, P = 0.01; ***, P < 0.001. |  |

TABLE 1. Reciprocal serum HAI antibody responses at 2 and 4 weeks postvaccination in healthy and infirm elderly patients immunized with the 1994–1995 Trivalent Influenza Vaccine