Vaccine Immune Response and Side Effects with the Use of Acetaminophen with Influenza Vaccine

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The purpose of this study was to determine whether acetaminophen impairs the immune response to influenza vaccine. Influenza vaccine is an under-utilized preventive measure, partly because of the unfounded perception that fever and myalgias frequently follow vaccination. While acetaminophen may decrease these infrequent side effects, it may also alter the immune response to vaccination. We compared the effect of acetaminophen with placebo on the humoral immune response to the 1991–1992 commercially available influenza vaccine. We studied 60 healthy, elderly subjects from a geriatric clinic and 20 infirm, elderly subjects from a nursing home. The subjects were randomly assigned to receive placebo or acetaminophen (1,000 mg every 6 h) for 2 days. Acetaminophen did not depress or enhance the immune development of serum hemagglutination inhibition antibody to the three vaccine antigens. The systemic side effects of fever and myalgia were uncommon in both groups. The healthy elderly subjects mounted a significantly better immune response to the influenza virus A/Taiwan/1/86 (H1N1) vaccine strain than did the infirm elderly subjects (geometric mean titer, 115 versus 51; P = 0.003). The functional activity score obtained by using the chronic healthy evaluation component of the Acute Physiology and Chronic Health Evaluation system could be used to distinguish the healthy from the infirm elderly (scores of 1.27 versus 3.75, P < 0.001). Acetaminophen neither depressed nor enhanced the serum antibody response to the vaccine in the healthy and infirm elderly subjects studied.

Influenza vaccine remains an underutilized preventive measure for decreasing the morbidity and mortality from influenza virus infection in the elderly (2). One of the reasons for underutilization is the perception that the flu syndrome follows vaccination. However, a recent controlled study failed to confirm this and showed that systemic symptoms occur in less than 1 to 2% of those vaccinated (17). In addition, the public is generally not aware that when an influenza epidemic is occurring, other respiratory infectious agents are present that may also cause the flu syndrome (6). The other respiratory infectious agents, such as rhinoviruses and parainfluenza viruses, may also cause fever and other symptoms at the same time that influenza vaccine is administered (9).

The use of antipyretics at the time of vaccination would probably reduce the incidence of fever and other systemic side effects, such as myalgias and malaise. Antipyretics, however, may affect the immune response to a vaccine. The medical literature has presented conflicting information on the effects of antipyretics on different aspects of the immune response. In vitro studies have considered the effect on lymphocyte blastogenesis, and in vivo studies have examined the effect on antibody formation. In small, clinically achievable doses, acetaminophen has been shown to enhance lymphocyte responses in vitro, while it is suppressive at higher doses (8, 18, 19).

If antipyretics can be used to prevent influenza vaccine side effects, it is necessary to determine whether antipyretics alter the immune response to influenza vaccine. Therefore, in a prospective, randomized, controlled trial, we compared the effects of acetaminophen with placebo on the humoral immune response to vaccine. We found that acetaminophen did not affect the serum antibody response to vaccine.

MATERIALS AND METHODS

We recruited 60 healthy, elderly subjects from the Cornell Geriatric Clinic in New York City, N.Y., and 20 infirm, elderly subjects from the Woodcrest Center in New Milford, N.J. Subjects were given the 1991–1992 commercially available influenza vaccine manufactured by Parke Davis and Company, Inc. The vaccine contained 50 μg of hemagglutinin for influenza virus A/Taiwan/1/86 (H1N1), for influenza virus A/Beijing/353/89 (H3N2), and for influenza virus B/Panama/45/90. The vaccine was given by intramuscular injection in the deltoid muscle. It was administered between late October and early November 1991. Most of the subjects had been immunized against influenza before.

Three blood specimens were obtained: at the time of vaccination, 3 weeks later, and at the end of the influenza season in April 1992. Serum hemagglutination inhibition (HI) antibody titers were determined at the Hackensack Medical Center Virology Laboratory. Virus strains were obtained from Nancy Cox and Helen Regnery, Centers for Disease Control, Atlanta, Ga. The HI test was performed according to methods described earlier (11, 12).

Subjects were randomly assigned to receive either acetaminophen or placebo immediately after vaccination. The acetaminophen group received 1,000 mg four times a day for 2

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days. A 1,000-mg dose was chosen instead of a 650-mg dose because the higher dose has a greater antipyretic effect. The placebo group received sugar-encapsulated tablets four times a day for 2 days. The medications were started at the time of vaccination. Acetaminophen (Tylenol) was manufactured by McNeil Consumer Products Co., Fort Washington, Pa. We did not record the prior use of antipyretics or analgesics by the study subjects. The subjects recorded information and reactions on a special form. The information included temperature (taken twice daily); systemic symptoms, such as muscle aches, weakness, or fever of 100°F (ca. 38°C) or higher; and local reactions, such as redness and tenderness at the vaccination site. The forms were returned to us for analysis, and appropriate use of acetaminophen or placebo was confirmed then.

Evidence of influenza virus in the community was monitored by the Hackensack Medical Center Virology Laboratory. Monitoring is done in order to determine whether there is an influenza epidemic in our patients' community and what type of strain is responsible for the epidemic. Four types of cells were used to demonstrate the presence of respiratory viruses in tissue culture: primary rhesus monkey kidney cells and serially propagated human cell lines MRC-5, HEP-2, and A549. Alulantoic egg inoculations were also done in an attempt to isolate influenza virus. The Directogen test (Becton Dickinson, Baltimore, Md.) was used to detect respiratory syncytial virus. Viruses were identified by previously described methods (11, 12, 15).

We used the chronic health evaluation scoring component of the first version of the Acute Physiology and Chronic Health Evaluation (APACHE) system to determine the severity of chronic diseases (10, 14). The four health categories were assigned numerical values as described previously (10) and discussed with Dr. Knaus. Patients were scored by one of the investigators (J. Bonelli), using the CHE component. The scoring system reflects differences in the ability of the subjects to carry out self-care functions.

Statistical analyses were performed with Student's t test for continuous variables and 95% confidence intervals (CIs) with SYSTAT (Systat, Inc., version 5.01, 1990).

**RESULTS**

The HI antibody responses of the 60 healthy, elderly subjects studied at the Cornell Geriatric Clinic are shown in Table 1. No significant differences were seen among the three antigens when we compared the immune responses in the acetaminophen and placebo groups.

The HI antibody response to influenza vaccine in the 20 infirm, elderly subjects at the Woodcrest Center is shown in Table 2. Again, there were no significant differences for two of the three vaccine strains. The higher postvaccination geometric

**TABLE 1. Serum HI antibody titers in healthy elderly subjects given influenza vaccine plus either acetaminophen or placebo**

<table>
<thead>
<tr>
<th>Vaccine strain and group</th>
<th>GMT</th>
<th>% of subjects with HI titer of:</th>
<th>% of subjects with 4-fold rise in titer after vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before vaccine</td>
<td>After vaccine</td>
<td>≥40 before vaccine</td>
</tr>
<tr>
<td>A/Taiwan/1/86 (H1N1)</td>
<td>54 114</td>
<td>Acetaminophen</td>
<td>67 100 93</td>
</tr>
<tr>
<td></td>
<td>62 116</td>
<td>Placebo</td>
<td>73 100 80</td>
</tr>
<tr>
<td>A/Beijing/353/89 (H3N2)</td>
<td>15 50</td>
<td>Acetaminophen</td>
<td>17 93 70</td>
</tr>
<tr>
<td></td>
<td>13 42</td>
<td>Placebo</td>
<td>10 77 60</td>
</tr>
<tr>
<td>B/Panama/45/90</td>
<td>32 66</td>
<td>Acetaminophen</td>
<td>52 100 79</td>
</tr>
<tr>
<td></td>
<td>31 57</td>
<td>Placebo</td>
<td>42 92 77</td>
</tr>
</tbody>
</table>

*Subjects from the Cornell Medical School Geriatric Clinic were immunized with the 1991-1992 trivalent influenza vaccine. In the acetaminophen group, there were 30 patients; mean age, 73 years; 52% males, 48% females; 97% previously vaccinated against influenza. In the placebo group, there were 30 patients; mean age, 75 years; 46% males, 54% females; 100% previously vaccinated against influenza.*

**TABLE 2. Serum HI antibody titers in infirm elderly subjects given influenza vaccine plus either acetaminophen or placebo**

<table>
<thead>
<tr>
<th>Vaccine strain and group (no. analyzed)</th>
<th>GMT</th>
<th>% of subjects with HI titer of:</th>
<th>% of subjects with 4-fold rise in titer after vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before vaccine</td>
<td>After vaccine</td>
<td>≥40 before vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/Taiwan/1/86 (H1N1)</td>
<td>40 49</td>
<td>Acetaminophen</td>
<td>71 100 100</td>
</tr>
<tr>
<td>Acetaminophen (7)</td>
<td>35 55</td>
<td>Placebo</td>
<td>55 100 82</td>
</tr>
<tr>
<td>A/Beijing/353/89 (H3N2)</td>
<td>11 25</td>
<td>Acetaminophen</td>
<td>11 71 43</td>
</tr>
<tr>
<td>Acetaminophen (7)</td>
<td>10 32</td>
<td>Placebo</td>
<td>0 78 56</td>
</tr>
<tr>
<td>Placebo (9)</td>
<td>47 128</td>
<td>Acetaminophen</td>
<td>67 100 100</td>
</tr>
<tr>
<td>B/Panama/45/90</td>
<td>26 55</td>
<td>Placebo</td>
<td>45 82 64</td>
</tr>
</tbody>
</table>

*Subjects from the Woodcrest Center Nursing Home were immunized with the 1991-1992 trivalent influenza vaccine. In the acetaminophen group (n = 9), seven subjects were analyzed for A/Taiwan and A/Beijing, and nine were analyzed for B/Panama; mean age, 88 years; 22% males, 78% females; 100% previously vaccinated against influenza. In the placebo group (n = 11), 11 subjects were analyzed for A/Taiwan and B/Panama and 9 were analyzed for A/Beijing; mean age, 85 years; 18% males, 82% females; 100% previously vaccinated against influenza.*
mean titer (GMT) observed for the influenza virus B/Panama strain in the acetaminophen group approached statistical significance (GMT, 128 versus 55; P = 0.07). This finding may be related to the fact that subjects randomly assigned to the acetaminophen group had a higher HI GMT before vaccination than did those in the placebo group (GMT, 47 versus 26; P = 0.24).

We noted some postvaccination differences when we compared the healthy, ambulatory, elderly subjects at the Geriatric Clinic with the infirm, elderly subjects at the Woodcrest Center (Table 3). Although the healthy, elderly subjects began with a higher GMT for influenza virus A/Taiwan before vaccination than the nursing home subjects, the difference was not significant (GMT, 60 versus 36; not significant [NS]). The healthy elderly, however, developed a significantly higher response after vaccination (GMT, 115 versus 51; P = 0.003). The healthy elderly subjects also had a significant rise in titer from 60 to 115 (P < 0.002), while the infirm elderly subjects did not (rise in titer from 36 to 51; NS). The GMT for the influenza virus A/Beijing strain did not rise as high in the infirm elderly subjects after vaccination as it did in the healthy elderly subjects (GMT, 28 versus 46; P = 0.07). For the influenza virus B/Panama strain, there were no apparent differences between the two groups. The immune responses in the healthy elderly subjects were comparable to those observed in children and young adults with cystic fibrosis.

We scored the subjects' functional activity by using the chronic health evaluation component of the original APACHE scoring system (14). The mean score for the healthy, elderly subjects at the Geriatric Clinic was 1.27 (CI, 1.15 to 1.38), while the mean score of 3.75 (CI, 3.54 to 3.96) for the infirm, elderly subjects at the Woodcrest Center was significantly higher (P < 0.001).

Our community respiratory virus monitoring program for children identified 27 influenza virus A/Beijing-like strains between late November 1991 and early February 1992. Forty-one respiratory syncytial virus isolates were found during the same time period. In addition, nine parainfluenza viruses (seven parainfluenza type 2), one influenza virus type B, one adenovirus, one herpes simplex virus type 1, and one coxsackievirus type B1 were isolated. The last influenza virus was isolated in early March 1992.

The postepidemic blood specimens drawn in April 1992 were examined for serologic evidence of infection. The postvaccination serum specimens were compared with the postepidemic sera. No fourfold or greater rises in HI antibody titers were observed for the healthy, elderly subjects during the epidemic period. Although HI antibodies in the sera of three infirm, elderly subjects rose significantly, none of the three subjects had flu symptoms. The postvaccination and postepidemic HI titer for the three subjects were 10 and 640, 5 and 80, and 20 and 80, respectively.

The April serum specimens collected from all subjects were compared with the postvaccine serum specimens in order to examine the longevity of the immune response in the placebo and acetaminophen groups. A less than twofold drop in titer occurred. No clinically apparent or statistically significant differences were noted when comparing the acetaminophen group with the placebo group for either the healthy or infirm elderly subjects.

Vaccine effects occurred somewhat more frequently in the placebo group. The difference, however, was not statistically significant. Among the 39 acetaminophen recipients, local tenderness at the injection site occurred in 3 (7.7%) and fever in 1 (2.6%) subject. Among the 41 placebo recipients, local tenderness occurred in 3 (7.3%), fever in 3 (7.3%), and myalgia in 1 (2.4%) subject.

### DISCUSSION

The effect of antipyretics on the immune response is controversial. Some studies indicate that lymphocyte blastogenesis is affected by acetaminophen. In one study, blastogenesis was enhanced by 100% at an acetaminophen dose of 200 μg/ml but was inhibited by 50% at 500 μg/ml (18). The enhancing effect of acetaminophen occurred only when the drug was in contact with cells during the early period of cell activation (19). In addition to the effect on cell-mediated immunity, Graham et al. showed that the immune response to rhinovirus infection was less robust in persons who received acetaminophen or nonsteroidal anti-inflammatory agents (8). The administration of acetaminophen was associated not only with reduced titers of serum neutralizing antibodies after experimental or natural rhinovirus infection but also with greater clinical severity of upper respiratory symptoms and increased duration of virus shedding in nasal secretions. Long et al. studied the effect of acetaminophen on the antibody response to diphtheria, tetanus, and pertussis vaccine (16). In contrast to the previous
findings (8), Long et al. found that acetaminophen did not alter the antibody response to this vaccine.

Acetylsalicylic acid (ASA) has also been shown to impair blastogenesis (3, 18). In contrast, Smith et al. showed that lymphocyte blastogenesis was not reduced by ASA (21). Rhinovirus shedding is prolonged in persons taking ASA during experimental rhinovirus infection (8, 22). In addition, Graham et al. showed that antibody response was decreased by ASA (8).

Other nonsteroidal anti-inflammatory drugs have various effects on the immune response. Decreased blastogenesis has been described for ibuprofen as well as other such agents (8, 18). In addition, Graham et al. showed decreased antibody response to rhinovirus infections with ibuprofen (8). By contrast, Day (4) predicted an increase in the immune response with the use of nonsteroidal anti-inflammatory drugs because they inhibit prostaglandin E-2 synthesis. Since prostaglandins inhibit lymphocyte activity, Day deduced that by decreasing prostaglandin synthesis, lymphocytes would be stimulated and enhance the immune response.

We found no effect on the serum immune response to influenza vaccine when acetaminophen was used as an antipyretic for 2 days.

The differences observed in antibody response between healthy and infirm elderly subjects confirm our previous findings that the infirm elderly have an impaired immune response to some vaccine strains (10). We also confirmed a high score for the chronic health evaluation component of APACHE as a surrogate marker for the elderly group exhibiting an inferior immune response to influenza vaccine (10). Phair et al. also demonstrated an impaired immune response in infirm, elderly subjects (20). The reason for the decrease in immune response may relate to the interleukin-2 depletion seen in elderly individuals. Huang et al. proposed that depletion of interleukin-2 in the infirm elderly may prevent them from developing an adequate immune response to an administered antigen (13).

Systemic side effects from the influenza vaccine were infrequent in both groups, although somewhat less in the acetaminophen group. As the incidence of side effects after influenza vaccination is normally small, our ability to detect a statistically significant reduction in the acetaminophen group may have been limited by our small sample size (5). In the study by Margolis et al. (17), the incidence of systemic symptoms was low. Feverishness occurred in 5.7% in the vaccine group and 4.2% in the placebo group, a difference of 1 to 2% (NS). Actual temperatures were not determined.

Margolis and colleagues also studied injection site reactions in the elderly (17). Only local tenderness differed significantly when the vaccine and placebo groups were compared. Among individuals receiving the vaccine, 20.1% experienced local tenderness at the injection site, compared with 4.9% in the placebo injection group. The incidence of local tenderness in our study was between 7 and 8% in both groups. Our incidence rates were too low to expect to see significant differences in our small sample. Therefore, we cannot conclude that acetaminophen reduces vaccine side effects.

Our observations have potential clinical importance. Although the incidence of systemic side effects after influenza immunization is small, on the order of 1 to 2% or less, clinicians are still likely to prescribe antipyretics such as acetaminophen for side effects that they anticipate despite evidence to the contrary (1, 7). In addition, people are likely to take antipyretics to prevent anticipated side effects. It is important to determine whether acetaminophen can be used to inhibit the anticipated side effects of influenza vaccine without adversely affecting the humoral immune response to influenza vaccine. If this information helps improve the acceptance of influenza vaccine and increases the number of elderly persons receiving the vaccination, then the observations made here will have been useful. Further studies should be done with larger groups to confirm our findings.

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REFERENCES


