Effect of Prednisone on Response to Influenza Virus Vaccine in Asthmatic Children

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Objective: To evaluate the immunogenicity of the influenza virus vaccine in children receiving short-course (a burst) prednisone therapy for acute asthmatic exacerbations.

Design: Prospective cohort study.

Setting: Outpatient pediatric clinic of a military medical center.

Patients: Children aged 6 months to 18 years requiring the 1996 influenza virus vaccine were eligible for the study. A total of 58 children were enrolled initially. The control group included 37 asthmatic children requiring less than 900 µg/d of inhaled prednisone and their siblings. The prednisone group included 21 children vaccinated at the beginning of a course of prednisone prescribed to treat an asthma exacerbation. Thirty-one control subjects (84%) and 19 patients in the prednisone group (90%) completed the study. Dropout was due to failure to come in for the postvaccination serum sampling.

Interventions: All study patients underwent immunization with the 1996-1997 trivalent subvirion influenza virus vaccine (FluShield; Wyeth Laboratories Inc, Marietta, Pa) containing 15-µg hemagglutinin antigens each of A/Texas/36/91 (H1N1)(A/H1), A/Wuhan/359/95 (H3N2)(A/H3), and B/Beijing/184/93 (B). The prednisone cohort received a burst of oral prednisone therapy (2 mg/kg per day for 5 days).

Main Outcome Measures: To assess the immunogenicity of the vaccine between both groups, at least a 4-fold rise in titer and end titers of at least 1:40 to each of the 3 antigens were compared. Mean changes in geometric titers to the 3 antigens were also compared.

Results: Proportion of patients in each group with at least a 4-fold rise in titer to each of the influenza antigens was as follows: for A/H3N3 antigen, 15 patients (79%) in the prednisone group vs 22 controls (71%) (P = .74); for A/H1N1 antigen, 16 patients in the prednisone group (84%) vs 20 controls (64%) (P = .20); and for B antigen, 7 patients in the prednisone group (37%) vs 8 controls (26%) (P = .53). Proportion of patients in each group with an end titer of at least 1:40 to each of the antigens was as follows: for A/H3N2 antigen, 18 patients in the prednisone group (95%) vs 28 controls (90%) (P = .69); for A/H1N1 antigen, 17 patients in the prednisone group (89%) vs 26 controls (84%) (P = .99); and for B antigen, 7 patients in the prednisone group (37%) vs 13 controls (42%) (P = .99). There were also no significant differences between groups in the mean changes in geometric titers to any of the 3 antigens.

Conclusions: Prednisone bursts did not diminish the response of asthmatic children to the 1996 influenza virus vaccine, compared with controls. Children can be effectively vaccinated against influenza virus while they are receiving prednisone therapy bursts for asthmatic exacerbations.


Editor’s Note: Another supposed reason NOT to immunize against influenza goes down the drain. I hope this leads to more asthmatics receiving the recommended vaccine.

Catherine D. DeAngelis, MD

Infection with the influenza virus is a substantial cause of morbidity and mortality worldwide. Each winter, influenza virus infections account for a significant proportion of health care visits. Asthmatics with moderate to severe disease are considered to be at a higher risk for serious sequelae of influenza virus infection. Fortunately, a safe and efficacious influenza virus vaccine is available and recommended annually for protection of these patients. Unfortunately, the overall immunization rate against influenza virus for asthmatic children is less than 10%. This poor compliance rate may be because many patients receive health care only when they are ill, whereas they neglect to keep appointments for preventive care. Therefore, withholding influenza virus vaccination from patients who present with acute asthma represents a missed opportunity to vaccinate. Vaccination rates would improve if health care workers were to administer influenza virus vaccine to children presenting with an exacerbation of their asthma.

However, many health care practitioners are concerned about a possible sup-
PATIENTS AND METHODS

PATIENTS

From October 1 to December 31, 1996, children aged 6 months to 18 years with a known diagnosis of moderate to severe asthma and their siblings who presented to Madigan Army Medical Center Pediatric Clinic, Tacoma, Wash, were invited to participate in the study. All children met criteria for routine vaccination against influenza on the basis of a known history of moderate to severe asthma or being the sibling of an asthmatic child. Asthmatic children who did not require a glucocorticoid burst at the time of influenza vaccination and their healthy siblings comprised the control group. The prednisone group consisted of asthmatic children presenting to the clinic with an acute exacerbation of asthma requiring treatment with glucocorticoids. These patients started a 5-day course of prednisone or prednisolone (2 mg/kg per day) within 48 hours of enrollment into the study. Children were excluded from the study if they had a known contraindication to influenza virus vaccination or known immunocompromise or had received oral or intravenous glucocorticoid therapy within the 3 weeks preceding enrollment. Asthmatic subjects requiring greater than 900 µg/d inhaled glucocorticoids or long-term oral glucocorticoid therapy were also excluded, since the scope of our study was not large enough to address the potential effects of long-term glucocorticoid use on the influenza virus vaccine response.

All children were immunized using standard methods with the trivalent subvirion influenza vaccine (FluShield; Wyeth Laboratories Inc, Marietta, Pa; lot 4968264) containing 15-µg hemagglutinin antigens each of A/Texas/36/91 (H1N1)(A/H1), A/Wuhan/359/95 (H3N2)(AH3), and B/Beijing/184/93 (B). This product was not subject to the potency. In accordance with the guidelines of the American Academy of Pediatrics for immunization against influenza, patients who were younger than 9 years and had not received an influenza virus vaccination previously received a booster dose after a 4- to 6-week interval. Prevaccination serum samples were obtained from each subject on enrollment, and postvaccination samples were obtained 3 to 6 weeks after the last vaccination dose. Children were monitored in the clinic for 20 minutes after vaccination for severe reactions. Parents were instructed to note any reactions to the immunization within the first 24 hours, including injection-site pain and fever. On the follow-up visit for the final serum sampling, any immunization reaction and interim illnesses and asthma exacerbations during the study were recorded by the investigators. Compliance with glucocorticoid dosing schedules was noted by asking the parents if any doses had been missed. The Madigan Army Medical Center Institutional Review Board approved this protocol for human use. Legal guardians for every patient gave informed written consent to participation in the study, as did each patient older than 9 years.

LABORATORY ANALYSIS

Serum samples were frozen, paired, and shipped to the Influenza Branch, Centers for Disease Control and Prevention, Atlanta, Ga, for analysis. Samples collected from both groups before and after vaccination were identically treated with receptor-destroying enzyme, and all samples were assayed using the hemagglutination inhibition (HAI) test with standard methods. The HA antigen for B/Harbin/07/94 was treated with ether to obtain optimal sensitivity. Serum samples were run simultaneously in pairs. We defined an immunologic response as a titer rise of at least 4-fold from baseline. Starting dilutions of HAI were set at 1:5. A postvaccination titer of at least 1:40 was considered a protective response. Although the exact correlation between an absolute HAI serum titer and protection is unclear, there is evidence that a titer of at least 1:40 confers protection against influenza virus infection. Previous studies also have used this level as a marker for protection.

STATISTICAL ANALYSIS

The Fisher exact test was used to analyze race and sex differences and to compare the proportion of patients in each group achieving an immunologic postvaccination titer of at least 1:40. The Fisher exact test was also used to compare the proportion of patients in each group requiring booster doses. Because of the geometric nature of the titer assays, titer responses were expressed as the difference between prevaccination and postvaccination log₂ (titer/5) for each patient. Mean values for the group were obtained for the purpose of comparison. For example, a change in titer response in a patient from 1:40 to 1:160 would be expressed as 2. Mean titer rises, mean age, and mean number of days between last vaccine dose and serologic sampling were evaluated using the unpaired t test. For a protective end titer of at least 1:40, our study had a power of 0.8 to detect a difference of greater than 34% between the prednisone and control groups for the A/H1N1 antigen, a difference of greater than 37% for the A/H3N2 antigen, and a difference of greater than 34% for the B antigen. The power analysis was performed using an α of .05 and normal approximations for a 2-sided test.

pressed response to the influenza virus vaccination among asthmatics who require a short course (a burst) of high-dose glucocorticoids for treatment of an asthma exacerbation. The manufacturer’s insert for the influenza virus vaccine highlights this concern with a warning that “patients with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including . . . corticosteroids . . . ) may have a reduced antibody response . . . .” Since the parenteral influenza virus vaccine is not a live virus, there is no specific contraindication to concurrent administration in patients receiving high-dose glucocorticoids, but concern over the effect on immunogenicity remains.

We hypothesized that administration of short-term glucocorticoid therapy would not diminish antibody responses of asthmatic children to the influenza virus vaccine. We evaluated the immunogenicity of the vaccine when administered to children receiving a burst of high-dose prednisone for treatment of their asthma...
compared with a group of control children who did not receive prednisone.

## PATIENTS

From October 1 to December 31, 1996, we enrolled 58 children. Fifty patients completed the study, including 19 in the prednisone group and 31 in the control group. There were no significant differences between groups for sex, age, race, or percentage of children without a history of immunization against influenza (Table 1). The mean interval between the last vaccination and serologic sampling for the postvaccination titer was 33.4 days for the prednisone group and 32.3 days for the control group ($P = .63$). Both groups reported less than 3% incidence of adverse effects to the vaccination. The most frequent adverse event in each group was tenderness at the injection site. No patients in either group had worsening in their asthma symptoms following the immunization. We observed no significant increase in use of asthma medications following the vaccination. Following immunization, 4 patients required interim prednisone bursts before obtaining the postvaccination titer; 3 children were in the prednisone group and 1 child was in the control group ($P = .15$). Each of these prednisone bursts was prescribed more than 2 weeks after the initial vaccination. Excluding these 4 patients did not alter the results of the statistical analysis.

All of our subjects had their postvaccination serum samples drawn later than November 25, 1996, ie, after the onset of the influenza season in Washington State. Influenza activity in Washington State during the 1996-1997 season began earlier than usual, with peak number of cases occurring from November 25 to December 19. Seventy-six percent of influenza cases isolated by the Washington State Department of Health, Seattle, during the season were attributable to A/H3N2 antigen, 24% to B antigen, and none to A/H1N1 antigen. The influenza B antigen cases did not occur until late December. The influenza A/H3N2 and B strains isolated in the United States during the 1996-1997 season were antigenically similar to the strains included in the 1996-1997 vaccine. Since all of our subjects underwent postvaccination serologic study after the onset of influenza season, some of the study participants may have been infected, thus affecting their titer results. To evaluate for this possibility, we analyzed data on interim illnesses between groups. Five subjects (16%) in the control group and 4 subjects (21%) in the prednisone group experienced interim illnesses between initial immunization and the postimmunization titer. This did not represent a significant difference. All of the illnesses were respiratory and included otitis media ($n = 1$), sinusitis ($n = 2$), mild upper respiratory tract infection ($n = 2$), and asthma exacerbation ($n = 4$). None of the illnesses were clinically suggestive of influenza. Viral washings for influenza culture were submitted for 1 of the patients with an upper respiratory tract infection, with negative results for influenza virus. Excluding data from these patients from analysis did not alter the results of the study.

## SEROLOGY

There were excellent responses in both groups to the A/H1N1 and A/H3N2 antigens, but the response to the B antigen in both groups was poor. There were no statistically significant differences in the responses of both groups to the 3 components of the vaccine in the proportion achieving a 4-fold rise in titer (Figure 1) or the proportion with protective titers of at least 1:40 (Figure 2). The prednisone group actually had greater immunologic responses to all 3 components of the vaccine, but these did not reach statistical significance.

Both groups had strong quantitative titer rises to the A antigens, with a weaker response to the B antigen (Table 2). Although the differences between groups in mean titer rise to the 3 antigens were not statistically significant, there was a trend toward a better response to the A/H1N1 antigen in the prednisone group. There were no significant differences in the proportion of patients in each group with prevaccination titers of less than 1:40 to both of the A antigens. For A/H3N2 antigen, 20 con-

### Table 1. Demographic Characteristics of Subjects*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Prednisone Group†</th>
<th>Control Group†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>15 (79)</td>
<td>19 (61)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>15 (79)</td>
<td>26 (84)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (16)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (5)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>9.8 (4.0)</td>
<td>9.3 (4.4)</td>
</tr>
<tr>
<td>Patients without history of influenza virus vaccination</td>
<td>3 (16)</td>
<td>4 (13)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as number (percentage) of patients.
†Groups are described in the “Patients” subsection of the “Subjects and Methods” section.

### Figure 1

Percentages of patients with at least a 4-fold rise in antibody titer. Ninety-five percent confidence intervals for the A/H3N2, A/H1N1, and B antigens are as follows: for the prednisone group, 55% to 93%, 60% to 97%, and 16% to 62%, respectively; for the control group, 55% to 87%, 48% to 82%, and 11% to 41%, respectively. There was no significant difference between groups for any antigen ($P = .74$, $P = .20$, and $P = .53$, respectively).

### Figure 2

Percentages of patients achieving protective titers. Ninety-five percent confidence intervals are as follows: for the prednisone group, 55% to 93%, 60% to 97%, and 16% to 62%, respectively; for the control group, 55% to 87%, 48% to 82%, and 11% to 41%, respectively. There was no significant difference between groups for any antigen ($P = .74$, $P = .20$, and $P = .53$, respectively).
immune system interact to protect against influenza virus infection. Specific antibody against the hemagglutinin antigen is necessary for protection, and the formation of these antibodies is T-lymphocyte dependent.11 As the extent and scope of immunosuppression in humans receiving 5- to 10-day bursts of high-dose oral prednisone is still unclear, there is some concern that this therapy might interfere with a successful response to influenza virus immunization. Serum IgG levels in humans decline by 50% after 5 days of methylprednisolone administered at 16 mg/d,12 and large doses of glucocorticoids can cause lymphocytopenia and reduction in cytolysis.13 Delayed-type hypersensitivity also decreases, although this is due to decreased macrophage recruitment rather than impaired T-cell function.14 Despite these detrimental effects on humoral and cellular immunity, other studies have shown that there is no inhibition of primary or secondary responses to antigens in humans taking high-dose glucocorticoids.15 Claman16 has shown that patients who were taking 15 to 20 mg/d of prednisone had a normal response to immunization.

There has been only 1 other prospective study that assessed the antibody responses to the influenza virus vaccine in asthmatic patients receiving bursts of high-dose prednisone therapy for asthma exacerbations compared with controls. In that study, Park et al17 found no differences in the antibody responses to the A/H3N2 and A/H1N1 antigens between both groups and no difference in the rate of adverse events. However, they found a significantly better response to the B antigen in their prednisone group. Two other studies of children with asthma receiving long-term daily prednisone therapy also failed to find an association between prednisone and vaccine failure.18,19

Several studies have assessed the immunogenicity of the influenza vaccine in other patient populations exposed to glucocorticoids. Chalmers et al20 conducted a placebo-controlled study that evaluated the immunogenicity and safety of the influenza virus vaccine in patients with rheumatoid arthritis. One of the groups consisted of patients receiving immunosuppressive therapy, including daily prednisone use of greater than 7.5 mg/kg. There was no difference in the response to the vaccine between this group and healthy age-matched controls. Studies investigating influenza virus vaccine response in adults receiving steroids and other immunosuppressive agents documented a decreased
response to the vaccine, but the effect may have been due to the other immunosuppressive agents.21,22 Mauch et al20 investigated the response of children with solid organ transplants to the influenza virus vaccine using healthy siblings as controls. Many of these patients were receiving prednisone, 0.5 to 1 mg/kg per day, in addition to other immunosuppressive agents. There was no difference seen between controls and patients who had undergone transplantation, and regression analysis did not demonstrate that prednisone use correlated with response.

Immunization against influenza virus infection in children with asthma is recommended by the American Academy of Pediatrics. It has been demonstrated that even with the use of tracking systems to provide influenza virus vaccine to children with asthma, the immunization rates have been poor.3 Factors that affect parental compliance with the vaccination include providers’ attitudes and recommendations.23 Parents and providers may perceive that adverse effects of the vaccine will be more likely during an acute asthmatic exacerbation. However, several other studies have demonstrated that the influenza virus vaccine does not cause an increase in asthmatic symptoms,17,24,25 and this was also the case with our study. Also, the providers may be hesitant to trust the immunogenicity of the vaccine when given in conjunction with glucocorticoid bursts. The results of our study suggest that barriers to influenza immunization during an asthmatic exacerbation are unnecessary. Discarding these barriers should be an effective step toward improving overall compliance rates with the vaccine.

Drawbacks to our study include the use of inhaled glucocorticoids, limited numbers of subjects, and the concern that the study was not completed before the onset of the influenza season in Washington State. Although we did not exclude patients receiving inhaled glucocorticoids from the study, we did exclude patients who received doses that were potentially physiologic. The number of subjects enrolled was small but sufficient on power analysis to detect a clinically significant difference in response to the A antigen. Another limitation of our study is that all of the postimmunization serum samples were obtained after the onset of the influenza season. The response to the vaccination may have been augmented in some cases by natural infection. However, analysis of clinical data on all subjects failed to demonstrate any subjects with clinical evidence of acute influenza during the study. In addition, since Washington State reported only influenza A/H3N2 infections during our study, there should have been no potential effect on the outcome in our patients’ responses to A/H1N1 or B antigen.

The results of our study suggest that the influenza virus vaccination can be safely and effectively administered to asthmatic patients receiving prednisone bursts. Thus, children with asthma presenting to clinics or emergency departments with asthma exacerbations should be offered the influenza virus vaccination.