Persistence of protective immunity after postexposure prophylaxis of varicella with oral aciclovir in the family setting

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Abstract
The persistence of protective immunity after postexposure prophylaxis against varicella using oral aciclovir was evaluated in the family setting. Sixty one of 78 recipients of oral aciclovir were assessed by questionnaire, and 13 of 61 were evaluated for serum antibody to varicella zoster virus (VZV) using the fluorescent antibody to membrane antigen method. The observation period ranged from 33 to 50 months. None of those (n = 44) who had initially seroconverted to VZV after aciclovir prophylaxis developed breakthrough varicella. All 13 who had serology repeated still had titres $\geq 4$. Antibody titres in those who had histories of re-exposure to the virus were significantly higher than in those who had not (p<0.01).

Keywords: aciclovir; postexposure prophylaxis; varicella; persistence of immunity

Varicella results from primary infection of a susceptible individual with varicella zoster virus (VZV). Although generally a mild disease, it can be complicated by bacterial superinfection of skin lesions, pneumonia, encephalitis, Reye's syndrome, or congenital varicella syndrome. The incidence of varicella is extremely high in children after exposure at home. Moreover, the clinical course in these children is generally more severe.1 It has been possible to prevent or modify the disease in the family setting by giving varicella zoster immune globulin,1 or live varicella vaccine,2 to children within 96 or 72 hours, respectively, of exposure. There has been, however, no procedure to prevent or modify the clinical course of varicella late in the incubation period. Recently, we reported successful prophylaxis with oral aciclovir after exposure late in the incubation period of varicella.3–6 The efficacy of this procedure has been previously confirmed by other laboratories.7–9 In Japan, many parents would like to protect their children from natural varicella, so this method would be one option for preventing secondary cases of varicella after exposure at home. It is not clear, however, whether the patients who receive oral aciclovir prophylactically have the same degree of long term immunity as untreated patients. If immunity in recipients of prophylaxis wanes, then this procedure may create a population of adults who are at risk of serious illness. Furthermore, the question of whether these patients are more susceptible to zoster than patients who have natural varicella has not been answered. Four years ago, we gave oral aciclovir to a series of children to prevent secondary varicella in the family. In the present study, we evaluate the protective efficacy of, and the persistence of immunity to, VZV after oral aciclovir prophylaxis.

Subjects and methods
STUDY POPULATION
The subjects were 78 children (41 boys and 37 girls), who were treated prophylactically with oral aciclovir between January 1992 and July 1993 in our hospitals. The median age of children was 1.7 years (range 1 month to 9 years) at the time of aciclovir prophylaxis. All of the children were given orally between 20 and 80 mg/kg daily of aciclovir in four divided doses for seven days, starting seven to nine days after exposure to the index case in their families. They were evaluated for immunity to VZV around two months after the prophylaxis.

CLINICAL FOLLOW UP
A letter was sent to parents of the children to explain the purpose of the study and to invite their child’s participation. The letter also requested parents to bring their child to our hospitals to collect blood to test for the VZV antibody. Questionnaires sent to the parents, requested details relating to any instance of varicella or herpes zoster among their family, playmates, nursery school, school, or other settings. They were also asked whether their children had contracted breakthrough varicella or herpes zoster since they had received oral aciclovir prophylaxis. A telephone interview was conducted to clarify the information in several cases.

SEROLOGICAL EXAMINATION
Humoral immunity to VZV was examined by the fluorescent antibody to membrane antigen method.10

STATISTICAL ANALYSIS
Student’s $t$ test was employed for statistical analysis. The statistical analysis was carried out using the logarithm of fluorescent antibody to membrane antigen titres.

Results
Replies to the questionnaire were obtained from 61 (35 boys and 26 girls) children. The median age of children was 1.8 years (range 3 months to 9 years) at the time of aciclovir prophylaxis. The
Antibody titres in cases 8 to 13 were significantly higher than those in cases 1 to 7 (p < 0.01).

† Represents age at the time of aciclovir prophylaxis.

* These three cases showed an antibody rise during the observation period.

Table 1  Clinical and immunological data of the 13 cases who had repeat serology approximately four years after aciclovir prophylaxis

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age† (years)</th>
<th>Sex</th>
<th>Dose of aciclovir (mg/kg/day)</th>
<th>Duration of observation period (months)</th>
<th>Re-exposure of varicella during the observation period</th>
<th>Antibody titre to VZV</th>
<th>As the time of convalescent phase of aciclovir prophylaxis</th>
<th>Four years after aciclovir prophylaxis‡</th>
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<tr>
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<td>50</td>
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</tbody>
</table>

*These three cases showed an antibody rise during the observation period.
† Represents age at the time of aciclovir prophylaxis.
‡ Antibody titres in cases 8 to 13 were significantly higher than those in cases 1 to 7 (p < 0.01).

Repeat serology was conducted in 13 of the 61 children who participated in the study (table). Each of the 13 individuals had an antibody titre of ≥ 4 (ranging from 4 to 64). There was a history of exposure to VZV during the observation period in six of the 13 cases, and in a half of these there was a rise in their VZV antibody titres. Seroconversion against VZV was not documented in either of these two cases at the time of the convalescent phase of aciclovir prophylaxis. Both patients had approximately 100 vesicles on their trunk and had a high fever.

None of the group who had received aciclovir prophylaxis developed herpes zoster during this observation period.

Discussion

Prophylaxis against varicella after exposure can be provided with varicella zoster immune globulin, live varicella vaccine, or aciclovir prophylaxis. Since our report on the efficacy of aciclovir prophylaxis in the family setting, there have been several further reports describing the benefits of this procedure. However, two major concerns have been raised. One is whether recipients of prophylaxis have impaired protective immunity, and the other is whether the incidence of zoster is higher in this group. This study was designed to address the former question. The results obtained from this study are encouraging, although the numbers studied are limited. None of those who had aciclovir prophylaxis developed breakthrough varicella presented with breakthrough varicella, and all of those who had repeat serology at the end of the observation period had titres ≥ 4, although the numbers studied were small. These results suggest that if the recipient acquires antibody to VZV after receiving aciclovir, then humoral immunity in the recipient will persist for at least three years. An assessment of the effects of aciclovir dose and clinical features at the time of the prophylaxis on the persistence of immunity against VZV would require a further prospective study controlled against patients not receiving aciclovir.

Since seroconversion to VZV is observed in only 84% of recipients of aciclovir prophylaxis, the remainder remain at risk of varicella. We therefore recommend that serology to VZV is checked in all aciclovir recipients and VZV vaccine given to those who do not seroconvert. Those re-exposed to varicella during the observation period had significantly higher antibody titres than those who were not. Re-exposure to wild type varicella, which is still endemic in Japan, is likely to have been important in maintaining antibody titres to VZV in these children. It has been reported that anti-VZV antibody titres in children immunised with VZV vaccine increase with time after immunisation. It is possible that antibody titres to VZV among aciclovir prophylaxis recipients will also increase with time.

In this study, two recipients (case 8 and case 10) were found to have seroconverted to VZV during the observation period. Neither had a clinical history of varicella, but had been re-exposed. It is possible that they had a low
concentration of VZV antibody during the convalescent phase of aciclovir prophylaxis which was not detected by our fluorescent antibody to membrane antigen test, and had protective immunity against breakthrough varicella. This suggests that better serological methods may be necessary to assess protection.

A longer and larger study would be necessary to assess the incidence of zoster in the recipients of aciclovir prophylaxis. Studies of immunocompromised children receiving aciclovir prophylaxis will also be important.

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