Antibody to Varicella-Zoster Virus After Passive Immunization Against Chickenpox

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Antibody titers to varicella-zoster virus were measured in varicella-susceptible immunocompromised children 48 h after they received either one of two lots of zoster immune globulin (ZIG) or a selected lot of immune serum globulin (ISG). Globulin was given to modify varicella in these children after exposure to varicella or zoster. Indirect immunofluorescence antibody titers (FAMA) of children after receipt of globulin ranged from <1:2 to 1:32. Geometric mean FAMA titers were highest after 1.2 ml of ISG per kg (FAMA titer 1:128) and 0.16 ml of ZIG lot A per kg (FAMA titer 1:024). Selected batches of ISG titering 1:128 or greater by FAMA, at a dose of 1.2 ml/kg, may be used to attempt to modify varicella in susceptible high-risk individuals when ZIG is not available.

Antibody titers to varicella-zoster (V-Z) virus, measured by the fluorescent antibody to membrane antigen (FAMA) technique in individuals immune to varicella, range between 1:2 and 1:64 (3, 6). Most immune individuals have a titer of 1:8 or 1:16. We were interested in determining the V-Z antibody titer of susceptible high-risk children who had been passively immunized against chickenpox to ascertain whether these children, who had no detectable antibody to V-Z virus of their own, would have detectable V-Z FAMA antibody after passive immunization. In addition we sought to determine whether initial serum levels of passively acquired V-Z antibody might have any bearing on the degree of modification of varicella. This report describes V-Z FAMA titers induced in children after passive immunization with either zoster immune globulin (ZIG) (4) or immune serum globulin (ISG) (5).

(This report was presented in part at the Sixth International Congress of Pharmacology in Helsinki, Finland, July, 1975 [A. A. Gershon and E. Smithwick, Abstracts, Sixth International Congress of Pharmacology, Abstr. no. 1173, 1975].)

MATERIALS AND METHODS

Antibody to membrane antigen of V-Z virus.
The FAMA immunofluorescence assay, as described previously (3, 6), is performed on unfixed tissue culture cells infected with V-Z virus. The infected cells are incubated with the serum or globulin to be tested, washed, and then incubated with fluorescein-labeled anti-human globulin. The cells are examined by fluorescence microscopy; a fluorescent halo is observed around infected cells if V-Z antibody is present in the serum or globulin being tested. In normal individuals, presence of this antibody correlates with immunity to varicella.

Sera and globulins. Serum specimens were obtained from immunocompromised children, believed to be at high risk to severe varicella. The underlying illness of these children included malignancy, deficiency of cellular immunity, and autoimmune diseases or nephrosis with high-dose steroid therapy. Sera were collected before passive immunization, approximately 48 h after passive immunization, and, where possible, weeks to months after passive immunization. Sera were stored at −20°C. Only children with no detectable V-Z antibody in their sera before passive immunization are included in this report. None of these patients had received recent blood transfusions.

Some patients were passively immunized with ZIG, lot A or lot B, produced by the Center for Disease Control in Atlanta, Ga. (W. A. Orenstein et al., submitted for publication). The V-Z FAMA titer of lot A was 1:024, and the titer of lot B was 1:512. The minimum dose aimed for was 0.125 ml/kg of body weight. In actuality, the average dose in the patients studied was 0.160 ml/kg for lot A and 0.150 ml/kg for lot B, with a range of 0.085 to 0.224 ml/kg. These patients were all given ZIG within 3 days of an intimate exposure to varicella or zoster.

Other high-risk patients were passively immunized with standard ISG, which had a V-Z FAMA titer of 1:128. Lots of ISG with this antibody were preselected by prior testing with the V-Z FAMA technique, since V-Z antibody titers of ISG may range from 1:16 to 1:256 (4). A dose of either 0.6 or 1.2 ml of this ISG per kg was used. The higher dose was approximately 10 times the volume of ZIG that would have been given. These children were given ISG within 3 days of exposure to V-Z virus rather than ZIG because no ZIG was available for them. This was usually either because the exposure was not considered intimate or because the national supply of ZIG was exhausted at the time.

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RESULTS

ZIG recipients. Of 22 children who were given ZIG lot A, none had detectable V-Z antibody before passive immunization, and all had detectable levels of antibody 48 h after passive immunization. The V-Z FAMA titers ranged between 1:4 and 1:32, and the geometric mean titer (GMT) for the group was 1:11.68 (Fig. 1). Of these 22 children, 10 developed mild clinical varicella, and 12 remained asymptomatic. Whether any developed subclinical disease is unknown.

Of 18 similar children who were given ZIG lot B, none had detectable levels of V-Z antibody before passive immunization and 15 had detectable levels of antibody 48 h after passive immunization. Their V-Z FAMA titers ranged between <1:2 and 1:16, with a GMT of 1:5.24 (Fig. 1). Of the three children with post-ZIG V-Z FAMA titers of <1:2, one had received a dose of 0.089 ml/kg, one received 0.157 ml/kg, and the third received 0.164 ml/kg. Two developed severe varicella accompanied by pneumonia; the third had no evidence of varicella. The child who had received the smallest dose of ZIG died.

Seven of the remaining 15 children with V-Z FAMA titers of ≥1:2 after receiving ZIG lot B developed mild varicella. Eight had no evidence of clinical varicella. Whether any of these children developed subclinical varicella is unknown (Orenstein et al., submitted for publication).

ISG recipients. Of seven children who were given ISG at 0.6 ml/kg, all had detectable V-Z antibody after passive immunization. Their V-Z FAMA titers ranged from 1:4 to 1:16 with a GMT of 1:7.25 (Fig. 1). None of these children developed clinical varicella or a persistent antibody titer suggesting subclinical varicella.

Of 13 children who were given ISG at 1.2 ml/kg, all had detectable V-Z antibody after passive immunization. Their V-Z FAMA titers ranged from 1:4 to 1:16 with a GMT of 1:9.39 (Fig. 1). Three of these children developed mild clinical varicella, and one developed subclinical infection as evidenced by a persistent V-Z FAMA titer for 8 months after passive immunization, although no symptoms of varicella occurred. Nine of the children had no clinical or serological evidence of having contracted varicella.

DISCUSSION

This study has shown that antibody to V-Z virus, measured by the FAMA technique, is detectable after passive immunization with ZIG.

![Fig. 1. V-Z FAMA titers (●) obtained, 48 h after passive immunization with ZIG or ISG, from patients susceptible to varicella. GMT (▲) are indicated for each type of passive immunization administered.](http://jcm.asm.org/Downloaded from http://jcm.asm.org/)

Informed consent was obtained from parents of all the patients in this study.
or selected batches of ISG. It is noteworthy that
the V-Z FAMA GMT was highest in the children
who were passively immunized with ZIG lot A.
Although there was a significant difference in
the GMTs of children who received ISG at a
dose of 1.2 ml/kg and children who received ZIG
lot A (P < 0.001 by Student’s t test), it can be
seen from Fig. 1 that there was considerable
overlap in titers produced. In addition, since
both GMTs fell between 1:8 and 1:16 it is likely
that the difference in GMTs was not truly sig-
nificant. Thus, whereas ZIG is the preferred
material for passive immunization of high-risk
individuals against varicella, one can expect to
produce detectable V-Z antibody in the blood
after a large dose of selected ISG as well, sug-
gesting that ISG will also modify varicella.

The lower dose of ISG, 0.6 ml/kg, did not
seem to be quite as successful as the higher dose
(1.2 ml/kg) in terms of the height of the titer
produced. Here the statistical difference be-
 tween ZIG B and ISG at 0.6 ml/kg and ZIG A
and ISG at 1.2 ml/kg probably is significant.
Nevertheless, antibody to V-Z virus was de-
tected by the FAMA technique in serum speci-
mens obtained from all children who received
the lower dose. The poorest response to passive
immunization was seen after ZIG lot B. This
batch of ZIG had a lower V-Z antibody titer than
most other lots of ZIG that have been used
(4).

Many of the children who received either ZIG
or ISG seemed to develop modified varicella. It
is impossible to conclude that passive immu-
nization with large doses of ISG was as successful
as that achieved with ZIG. However, since all
the children who received ISG had mild varicella
if they developed clinical disease, and since one
child had subclinical varicella after ISG, it is
likely that in certain high-risk hosts varicella
may be modified by giving selected batches of
ISG in large doses. This would seem to confirm
the previously mentioned data on V-Z antibody
titers 48 h after ZIG and ISG.

All of the children who developed varicella
had mild infections, with two exceptions. Two
children who received ZIG lot B developed se-
vere varicella with pneumonia, and one of these
children died of varicella. It is interesting that
the only children with severe varicella were
those who had no detectable antibody to V-Z
virus in their serum after passive immunization.

One child who received ZIG lot B had
no detectable antibody after ZIG was given, but
this child did not contract varicella.

Until recently, techniques with which to mea-
sure the V-Z antibody content of ISG were not
generally available. Now, however, a wide vari-
ety of such tests has been described, including
measurement of antibody to V-Z membrane an-
tigen by immunofluorescence (3, 6, 7) and the
immunoperoxidase technique (1) and by the im-
une adherence hemagglutination assay (2).

These tests are being performed in many med-
ical centers in the United States, and it is possible
to measure the level of V-Z antibody in batches
of ISG by these methods. Therefore, lots of ISG

titering 1:128 or higher for V-Z antibody could
be readily available to most medical centers for
use when ZIG is not available. It is theoretically
possible that the antibody in ZIG (i.e., after
zoster) differs from the antibody in ISG (i.e.,
after varicella) and that therefore ZIG and ISG
could differ in clinical efficacy. However, since
Ross (5) clearly demonstrated the capacity of
large doses of ISG to modify varicella in normal
persons this possibility seems, at the moment,
more theoretical than real.

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