Antibody to Varicella-Zoster Virus After Passive Immunization Against Chickenpox

ANNE A. GERSHON,* SERGIO PIOMELLI, MARGARET KARPATKIN,
ELIZABETH SMITHWICK, AND SHARON STEINBERG

Department of Pediatrics, New York University School of Medicine, New York, New York 10016

Received for publication 30 August 1978

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 1:1,024). 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 using 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 disease 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 1:1,024, 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.

Informed consent was obtained from parents of all the patients in this study.

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 $\geq 1:2$ 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.

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 significant. 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, suggesting 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 between 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 detected by the FAMA technique in serum specimens 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 immunization 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 severe 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 other 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 measure the V-Z antibody content of ISG were not generally available. Now, however, a wide variety of such tests has been described, including measurement of antibody to V-Z membrane antigen by immunofluorescence (3, 6, 7) and the immunoperoxidase technique (1) and by the immune adherence hemagglutination assay (2). These tests are being performed in many medical 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.

ACKNOWLEDGMENTS

The statistical analysis was performed with the aid of Angelo Ferrara. Secretarial assistance was provided by Maura Caruth and Maritza Colon.

This work was supported by Public Health Service grant AI-12814 from the National Institute of Allergy and Infectious Diseases.

LITERATURE CITED

1. Gerna, G., G. Achilli, and R. W. Chambers. 1977. Determination of neutralizing antibody and IgG antibody to varicella-zoster virus and of IgG antibody to membrane antigens by the immunoperoxidase technique. *J. Infect. Dis.* 135:975-979.
2. Gershon, A. A., Z. G. Kalter, and S. Steinberg. 1976. Detection of antibody to varicella-zoster virus by immune adherence hemagglutination. *Proc. Soc. Exp. Biol. Med.* 151:762-765.
3. Gershon, A. A., and S. Krugman. 1975. Seroepidemiologic survey of varicella: value of specific fluorescent antibody test. *Pediatrics* 56:1005-1008.
4. Gershon, A. A., S. Steinberg, and P. A. Brunell. 1974. Zoster immune globulin: a further assessment. *N. Engl. J. Med.* 290:243-245.
5. Ross, A. H. 1962. Modification of chickenpox in family contacts by administration of gamma globulin. *N. Engl. J. Med.* 267:369-376.
6. Williams, V., A. A. Gershon, and P. A. Brunell. 1974. Serologic response to varicella-zoster membrane antigens measured by indirect immunofluorescence. *J. Infect. Dis.* 130:669-672.
7. Zaia, J. A., and M. N. Oxman. 1977. Antibody to varicella-zoster virus-induced membrane antigen: immunofluorescence assay using monodisperse glutaraldehyde-fixed target cells. *J. Infect. Dis.* 136:519-529.