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Active immunization of children exposed to varicella infection in a hospital ward using live attenuated varicella vaccine given subcutaneously or intracutaneously

D Boda, Katalin Bartyik, P Szüts, S Turi

Paediatric Department of Szeged University School of Medicine, Szeged, Hungary

Active immunization using Takahashi OKA live attenuated varicella vaccine was carried out fire 5times to prevent the spread of "imported" varicella in a hospital ward. Susceptibility was previously tested by serological examinations: 14 children were vaccinated subcutaneously, the other 19 received the vaccine intracutaneously. Vaccination within a few days following exposure provided complete immunity in the great majority of cases. Intracutaneous administration was nearly as protective as the subcutaneous one.

Although an effective varicella vaccine has existed for ten years now [16] the problem of active immunization is still unsolved. This may partly be explained by the fact that varicella has been considered as a mild illness by both doctors and patients. Investigations in the past few decades revealed, however, that chickenpox can be dangerous and even lethal in immunosuppressed patients and in children in a poor condition due to a malignant disease [7, 8].

The first effective method to prevent varicella mortality was passive immunization by zoster immunoglobulin (ZIG) introduced by Brunnel et al [7, 8] and Gerson et al [9] to protect against varicella infection of patients with malignant disease treated with cytostatics. ZIG has a moderate therapeutic efficacy in actual and more serious varicella.

Passive immunization was a great step forward. It is, however, all the same important, especially in the above mentioned endangered cases, to investigate the possibilities of an active immunization. Takahashi et al [16] passaged varicella virus 11times on human embrional lung tissue, then 12times on guinea pig embryo cells and 2—5times on WI-38 type cells and the vaccine developed in this way has proved safe against varicella in susceptible children. The live attenuated vaccine was injected subcutaneously. Leukaemic and tumourous children were vaccinated with good results [11, 12, 13] with a similar vaccine, as it was shown by a series of detailed immunological examinations. Antileukaemic treatment was suspended for one week before and after vaccination.

The first reports were followed by a great number of vaccinations in hospitalized children suffering from malignant and different other diseases and in healthy children living in

closed communities or with their families [1, 2, 3, 4, 5, 10, 14, 15, 18]. They all proved that the Takahashi vaccine was harmless and produced nearly 100% seroconversion and immunity in healthy children susceptible to varicella. At least 80% safety could be achieved in case of recent contact with the virus in a hospital ward even after a few days incubation. Moreover, vaccinated patients developed no or only a mild form of the disease which means 100% protection against lethal manifestations. Recent studies have indicated that there is hope for the vaccine to be used with good results in the prevention of herpes-zoster, too.

Several decades ago a pioneering work was done in the field of active immunization against varicella by Ferencz, who recognized the intracutaneous immunizing effect of the fluid content of varicella vesicles and proved it by a number of appropriate epidemiological and complement binding methods. He called his procedure "varicellization". After the first results with live attenuated virus had been published, we called attention to those important early investigations [6].

The present examinations were focussed on the possibilities of active immunization to prevent the spread of varicella infection in a hospital ward.

Moreover we felt compelled to compare the results of the modern methods to those of Ferencz's examinations.

Patients and Methods

The investigations were carried out during five hospital epidemics due to imported varicella between December 22th, 1983, and July 3rd, 1984. They involved 39 children ranging in age from 3 months to 12 years, suffering from different diseases. None of them had malignant disease or leukaemia.

When varicella occurred in a ward, blood was taken from all the patients with a negative history for the illness to prove susceptibility by serological tests. Patients with no antibody response were vaccinated, the latest 36 hours after the manifestation of the first imported varicella. These children were divided into two randomized groups: parallel to each subcutaneous vaccination where 0.5 ml of Takahashi vaccine was used, one or two patients of the randomized group received 0.1 ml of the vaccine intracutaneously. No previous serological tests were done in nine cases and the vaccine was given only on the basis of the history. Later serological examinations showed that six of these nine patients had been exposed to chickenpox on an earlier occasion. Clinical follow-up examinations were done on the 10th post-vaccination day and one month later; blood samples were taken in some cases on the 10th day, otherwise one month after vaccination for antibody determinations. (Discharged patients were asked to come back for control.)

The vaccine used was the one labelled LOT 7906 containing the OKA strain live attenuated varicella virus developed by Takahashi et al [16] sent to us with prescriptions of control examinations. The vaccine arrived frozen in dry ice and was stored in the deep-freezer until assay.

The antibody titre was determined by ELISA (Enzygnost Varicella/Zoster Solid Phase Enzyme Immunoassay, Hoechst OSMK 03, Behringwerke AG, Marburg) using a Flow Titertek Multiscan (Eflab OY, Helsinki). The investigations were authorized by the Scientific Council and

the Research Ethical Committee of the Hungarian Ministry of Health. No vaccination was done without the informed consent of at least one parent.

Results

During the different hospital epidemics in our department a total of 96 children were found with a negative history for varicella. Real susceptibility was confirmed by serological examinations only in 33 cases. The other patients, although they were not vaccinated, did not get the disease even if they had contacted varicella patients.

Vaccination results are shown in Table I.

Neither local nor general reactions were recorded after subcutaneous vaccination.

Intracutaneous vaccination was followed, in some of the cases, by local reaction 7—10 days after injection, which corresponds to Ferencz's observations. Two patients developed erythema 2—3 mm in diameter, two others had vesicles of the size of a pinhead. In these latter cases no varicella vesicles were observed at any other area neither at that time nor later. None of the patients seroconverted on the 10th day following vaccination. One of the three children showed seroconversion at another test one month later. When immunity was checked one month after vaccination, the antibody response in the two groups was satisfactory, although the results of the subcutaneously vaccinated group were somewhat better (Table II).

At the same time none of the patients without elevation of antibody titre following vaccination developed varicella during the one month period of follow-up.

As it can be seen in Table I, varicella occurred in two subcutaneously vaccinated and in three intracutaneously vaccinated patients, on the 10th, the 12th, the 16th and two on the 17th day after vaccination.

The first subcutaneously vaccinated child who developed varicella on the 10th day must have been infected earlier. The other intracutaneously

Table I

Results of Immunization with Live Attenuated Varicella Vaccine

	Number of cases	
	subcutaneous vaccination	intracutaneous vaccination
No of vaccinated patients	14	19
Local reaction	0	4
General reaction	0	0
Seroconversion on 10th day	0/1	0/2
Seroconversion one month later	12/13	10/13
Mild or moderate varicella	2	3
Abortive varicella	0	2

Table II

Seroconversion following active immunization against varicella

Antibody titre	subcutaneous application	intracutaneous application
0	1	3
10×4^1	1	3
10×4^2	7	4
10×4^3	2	—
10×4^4	—	2
10×4^8	2	1
No of examined cases	13	13

vaccinated child presented with varicella on the 12th day had certainly been previously exposed to the disease since his brother who had not been hospitalized also contracted it. Traditional varicella was observed in one case in each group. It was considered to be mild in the intracutaneously vaccinated patients with only a few but definitely varicella vesicles. One patient of the intracutaneous group manifested abortive varicella first with sudamina-like vesicles, another one with several small papular eruptions. The only relationship between these signs and the vaccination was, however, the fact that we were extremely attentive to any such manifestation. Otherwise the incidence rate was the following: one case of varicella occurred in both vaccinated groups with each epidemic, which was an important factor proving that the children were in fact exposed to infection.

The six patients with earlier exposure to varicella (three vaccinated subcutaneously and three intracutaneously) had no local or general reaction and they did not develop manifest varicella. Their immune titre did not rise after one month, in one case it fell from 1 : 160 to 1 : 40.

Discussion

Special emphasis has been put on the need of an effective vaccine by the recent discovery of the possible complications of varicella. The great number of examinations reviewed have proved that the OKA vaccine of Takahashi is up to all such requirements. It has been demonstrated to be safe in patients with leukaemia and other malignant diseases. Still, as immunosuppressive cytostatics decrease the degree of immunization, it has been agreed that such patients must be tested serologically for immunity, and in case of susceptibility they should be given a temporary ZIG treatment until remission when active immunization can be done.

A great advantage of the vaccine is that, although it should be administered the soonest possible, it is effective even after exposure. Thus it can be of use for diminishing compli-

cations arising from imported infections regularly occurring in hospital wards. Unfortunately the chain itself cannot be broken, as one case of manifest varicella was always observed when immunization was done after exposure. The same consequence could be drawn from our rather limited investigations.

Administering the vaccine intracutaneously was not a novel idea but rather the reintroduction of Ferencz's examination, using now a well-tested vaccine and up-to-date serological methods. Our findings have confirmed the original observation in that a satisfactory degree of protection could be achieved with the virus given intracutaneously with one occasional vesicular eruption occurring at the injection site. No generalized symptoms appeared, and long term immunity was obtained.

The limited number of cases involved in the present investigation did not allow definite conclusions about the value of intracutaneously applied vaccination. In any case, intracutaneous vaccination seemed to be somewhat less effective than subcutaneous one. This lesser degree of protection does not necessarily ensue from the intracutaneous administration itself but rather from the smaller dose applied. In our latest examinations [17] 100% safety and seroconversion two weeks after vaccination were achieved using Ferencz's original vaccine derived from chickenpox vesicles. Further studies will decide on the degree of protection that might be obtained with a larger dose of vaccine given intracutaneously. It must also be considered whether any advantage may be achieved from the virus dermotropism manifesting itself at intracutaneous administration.

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D Boda MD
Pf 471
6701 Szeged, Hungary