

Persistence of rabies antibody 5 years after pre-exposure prophylaxis with human diploid cell antirabies vaccine and antibody response to a single booster dose

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SUMMARY

In 1978, 22 staff members of the National Institute of Virology, Pune, India, were given two doses of human diploid cell antirabies vaccine (HDCV) for primary pre-exposure prophylactic immunization; the interval between the two doses being approximately 4 weeks. Eighteen of these 22 vaccinees were given a booster dose 1 year later. All 18 vaccinees developed protective levels of antibody; most of them had antibody levels exceeding 10 IU/ml.

In 1984, 5 years after the booster dose, 11 (79.0%) of 14 vaccinees tested still possessed neutralizing antibody levels ranging from 0.5 IU/ml to 10 IU/ml. Fourteen days after the administration of a booster dose, the antibody levels ranged from 10 to ≥ 100 IU/ml for all except one vaccinee (5.2 IU/ml). These findings demonstrate that the majority of vaccinees retained detectable neutralizing antibody after pre-exposure prophylaxis for as long as 5 years and that a single booster dose thereafter evoked a good antibody response.

INTRODUCTION

Human diploid cell antirabies vaccine (HDCV) has proved to be very effective when used for post-exposure prophylaxis. There has been no reported case of rabies when the vaccine was used in the dosage schedule recommended for such prophylaxis together with rabies immune globulin (ACIP, 1984). The vaccine has also been shown to produce a good antibody response when administered in the schedule recommended in France for pre-exposure prophylaxis, i.e. primary immunization with two 1 ml doses injected 1 month apart followed by a booster dose a year later (Aoki *et al.* 1975).

There are few reports on the persistence of antibody to rabies virus for long periods after pre-exposure prophylaxis with HDCV (Roumiantzeff *et al.* 1984). This report describes the antibody response of laboratory personnel to pre-ex-

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posure prophylaxis, the persistence of antibody for 5 years and the effect of a single booster dose after this interval.

MATERIALS AND METHODS

Administration of the vaccine

Twenty-two staff members of the National Institute of Virology (NIV), Pune, who could have been exposed to rabies virus as part of their work, were each given two doses of HDCV obtained from the Institut Merieux, Lyon, France for primary immunization, followed by a booster dose after 1 year. The 1 ml doses were administered in accordance with the manufacturer's schedule for pre-exposure prophylaxis, except that the vaccine was inoculated by the intramuscular route in all vaccinees except one for whom the route was subcutaneous.

The interval between the first and second doses was 26–33 days for all except three vaccinees (19, 39 and 41 days, respectively); the mean was 29 days and the median was 28 days.

The interval between the second dose and the booster dose was 11·1 months to 13·2 months; the mean was 11·6 months, the median 11·5 months.

Almost 5 years after this booster dose (range: 4 years 10·1 months to 4 years 11·6 months) a further booster dose was administered by the subcutaneous route.

Collection of blood samples

A prevaccination blood sample was obtained on the same day as the first dose was administered. The interval between each dose and the collection of the respective blood sample was as follows:

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|---|---|
| (i) After the first dose | 26–33 days for all except three vaccinees (19, 39 and 41 days, respectively). |
| (ii) After the second dose | 30–39 days for all except 3 vaccinees (42, 50 and 100 days, respectively). |
| (iii) After the 1-year booster dose | 35–51 days |
| (iv) Between the booster dose and prior to the second (5-year) booster dose | 4 years 10·1 months to 4 years 11·6 months |
| (v) After the 5-year booster dose | Two blood samples obtained on the 7th and the 14th days, respectively. |

The blood samples were stored refrigerated for 24 h, after which the serum was separated from the clot. Aseptic procedures were followed at all stages. The sera were stored frozen at -20°C until they were despatched to the Institut Merieux, France, as samples coded with NIV specimen numbers only, where they were tested for neutralizing (N) antibody by the Rapid Fluorescent Focus Inhibition Test (Smith *et al*, 1973).

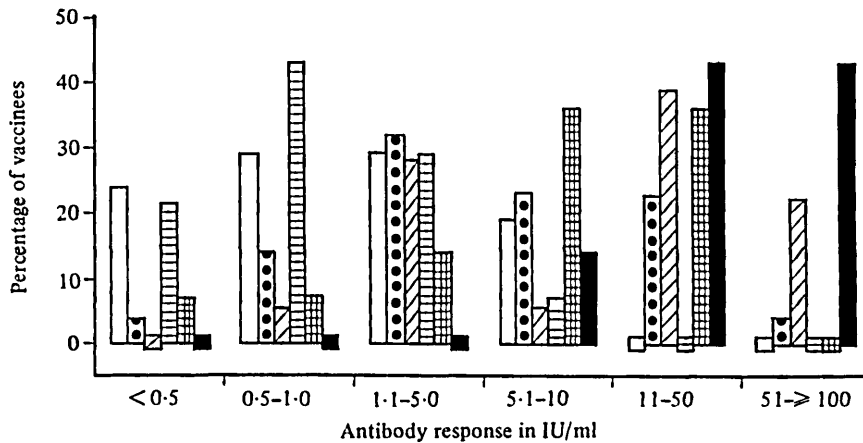


Fig. 1. Antibody response to HDCV and persistence of antibody. □, After first dose; ▤, After second dose; ▨, after first booster dose; ▩, persistence after 5-year interval; ▧, 7 days after second booster dose; ■, 14 days after second booster dose.

RESULTS

The antibody response after each dose and the persistence of antibody over a 5-year period are shown in Fig. 1.

Following the first dose, 16 (76%) out of 21 vaccinees (the serum sample of one vaccinee could not be obtained after the first dose) developed neutralizing antibody levels of 0.5 IU/ml or higher. Approximately half of the vaccinees (10 vaccinees, 48%) had N antibody levels between 1.1 and 10 IU/ml.

Following the second dose of the vaccine, all except 1 of the 22 vaccinees developed N antibody levels of 0.5 IU/ml or higher: the exception was a vaccinee with an equivocal antibody response (≤ 0.5 IU/ml), who had received his second dose within the recommended time interval after the first dose (33 days). Half of the vaccinees (11 vaccinees, 50%) had antibody levels exceeding 5 IU/ml; 6 of these 11 vaccinees had levels exceeding 10 IU/ml.

The geometric mean (GM) antibody levels rose from 1.9 IU/ml after the first dose to 5.9 IU/ml after the second dose.

A booster dose could be given to 18 of the 22 vaccinees. Following the booster dose, all 18 vaccinees had protective levels of antibody and all except 1 vaccinee (level 0.5 IU/ml) had N antibody levels exceeding 1.0 IU/ml. The majority (11 vaccinees, 61%) had antibody levels exceeding 10 IU/ml; 4 of these 11 vaccinees had levels exceeding 50 IU/ml. The GM antibody level was 10.2 IU/ml.

Of these 18 vaccinees, 14 could be tested for persistence of antibody approximately 5 years after the booster dose; 11 vaccinees (79%) still possessed N antibody levels ranging from 0.5 to 10 IU/ml (Fig. 1.). The GM antibody level was 1.3 IU/ml.

All 14 vaccinees, except 1, were found to have protective levels of antibody, 7 days after the administration of the second booster dose, given after the 5-year interval. The majority (10 vaccinees, 71%) had antibody levels between 5.1 and 50 IU/ml; 5 of these 10 vaccinees had levels exceeding 10 IU/ml. Fourteen days after the second booster dose all 14 vaccinees possessed high levels of antibody.

Except for one vaccinee, the antibody levels ranged from 10 IU/ml to ≥ 100 IU/ml (four vaccinees had levels of ≥ 100 IU/ml). The exception was the vaccinee in whose serum N antibody was not detected after 7 days; the antibody level in his 14th day serum was 5.2 IU/ml.

For these 14 vaccinees the GM antibody levels were 1.6, 5.6 and 11.0 IU/ml after the first, second and first booster doses, respectively. Five years later, the GM antibody level of 1.3 IU/ml was comparable to that after the first dose of the primary immunization schedule. On day 7 after the second booster, the GM antibody level of 8.5 IU/ml was comparable to that detected after the first (1 year) booster dose following the primary pre-exposure prophylaxis and on day 14 the GM antibody level of 36.1 IU/ml was more than threefold higher than that after the first booster dose.

DISCUSSION

Previous studies on the persistence of immunity after pre-exposure prophylaxis and the effect of a booster dose have been carried out after intervals of 2–3 years (Nicholson, Turner & Aoki, 1978; Plotkin, 1980). In one study, the effectiveness of a single booster dose 4 years after post-exposure prophylaxis with HDCV was demonstrated (Bahmanyar *et al.* 1976; Fayaz *et al.* 1981). The post-exposure prophylaxis in this study had consisted of one dose of rabies immune globulin and six doses of HDCV on days 0, 3, 7, 14, 30 and 90.

The most significant findings in our study are (a) in the absence of any further booster dose, 11 out of 14 vaccinees (79%) still had N antibody in levels of 0.5 IU/ml or higher 5 years after the previous dose; (b) of the remaining three vaccinees, two responded positively within a period of 7 days and the third within 14 days after the administration of a booster dose; (c) antibody levels rose markedly during this period with GM antibody levels rising from 1.3 to 8.5 IU/ml by day 7 and to 36.1 IU/ml by day 14; and (d) the GM antibody level on day 14 was more than threefold higher than that after the previous booster dose 5 years earlier.

At present there are two different recommendations for pre-exposure primary immunization. Some national authorities follow the US recommendation, which consists of a schedule of three doses of vaccine administered intramuscularly on days 0, 7 and 28; booster doses are generally recommended every 2 years, but may be given at shorter intervals to those in the higher risk groups, depending on neutralizing antibody levels. Other countries follow the pre-exposure prophylaxis recommendation proposed in 1974 in France and the UK which consists of a two-dose primary immunization schedule on days 0 and 28, followed by a booster dose 1 year later. A second booster dose is administered after 3–5 years.

Our findings demonstrate that this simple pre-exposure schedule, i.e. two initial doses, with an interval of 1 month between the doses, followed by a booster dose 1 year later, gives adequate immunity. A further booster is effective in inducing a good neutralizing antibody response even after an interval of 5 years.

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