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Intradermal pre-exposure rabies vaccine elicits long lasting immunity

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ABSTRACT

A retrospective cohort study of current rabies antibody titres from adults who received pre-exposure immunisation administered intradermally between 1994 and 2005, examining the decay in titre over time relative to the interval since last dose, and the total dose received. Participants receiving at least 0.6 ml total dose intradermally of vaccine over at least two clinic visits and all with three clinic visits, were shown to have an adequate titre with measurable levels of antibody indicating sero-conversion above 0.5 IU/ml, irrespective of the time interval since the last dose. No clear relationship was found between time interval since immunisation and the level of antibody. Using a schedule that administers 0.6 ml of rabies vaccine over three clinic visits the boosting interval could be extended towards ten years; substantially cheaper than the standard licensed intramuscular dosing schedule.

1. Introduction

Rabies is an acute viral encephalomyelitis caused by a lyssavirus, and is nearly always fatal. Infection is usually acquired following a bite from an infected animal host such as a bat or dog. Worldwide there are up to 70,000 human cases each year occurring mostly in developing countries such as India, where the virus is enzootic in certain animal reservoirs [1].

Rabies must be prevented as there is no effective treatment once symptoms are established. Vaccination before and after exposure is an important component of prevention. Pre-exposure prophylaxis is recommended for those working with at risk animals or patients likely to be infected with rabies, and those working or travelling in enzootic areas. There are currently two rabies vaccines licensed for use in the UK. A human diploid cell inactivated virus (HDCV) vaccine manufactured by Sanofi Pasteur MSD, and licensed for pre exposure prophylaxis by deep subcutaneous or intramuscular administration of 1 ml at each of days 0, 7 and 28, with further reinforcing doses at 2–3 yearly intervals if the subject remains at risk. "Rabipur" is also an inactivated virus vaccine, manufactured by Novartis. It is cultured in chick embryo cells. The dosing schedule is as for HDCV, but boosting is recommended at up to five-yearly intervals. The current (August 2007) price of a 1 ml vial of each vaccine type is £24.40, and thus £73.20 for a pre-exposure course [2].

Although unlicensed in the UK, several intradermally administered regimes have been evaluated for pre exposure immunisation and shown to produce an adequate response [3–6]. Lau and Sisson demonstrated that the effectiveness of the intradermal route does not vary according to age and gender, but commented on the need for experience in administration, and subsequent confirmation of titres by post immunisation serology [7]. The ability of the 0.1 ml dose of the HDCV vaccine to induce a uniformly protective antibody response has been questioned [8–10]. Cited reasons for this include inadequate technique failing to deliver the whole of the dose, use of low potency batches and leakage of the vaccine back up the needle track [11]. There is little documentation on the duration of protection following immunisation by the intradermal route beyond two years following immunisation [12].

Abbreviations: CI, confidence interval; GMT, geometric mean titre; HDCV, human diploid cell vaccine; IU/ml, international units per millilitre; $\ln_e$, natural logartithm; MSD, Merck, Sharp and Dohme Limited; FAVN, fluorescent antibody virus neutralisation test; WHO, World Health Organisation.

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Table 1
Antibody titres according to interval since last immunisation, total dose of vaccine received, and number of clinic visits

	n	Mean antibody titres (IU/ml)	Range (titres IU/ml)	Range (complete years)	Range (total dose)	Range (clinic visits)
Interval (complete years)						
12	1	0.87			0.4	1
11	3	3.34	1.50–5.92		0.2–0.6	1–3
10	4	20.67	1.14–70.15		0.4–0.6	2
9	9	2.71	0.22–7.79		0.4–0.6	1–2
8	9	21.27	0.22–121.5		0.2–0.6	1–3
7	8	2.77	0.38–10.26		0.2–0.6	1–3
6	6	22.39	0.38–121.5		0.4–0.6	1–2
5	4	5.2	2.60–10.26		0.4–0.6	1–3
4	13	0.98	0.13–3.42		0.4	1–2
3	10	2.49	0.06–17.77		0.2–0.4	1–2
2	9	0.48	0.06–1.14		0.3–0.4	1–3
1	12	82.83	0.06–830.88		0.4–0.8	1–4
0	1	1.14			0.4	2
Number of clinic visits						
1	37	5.29	0.06–121.5	1–12	0.2–0.4	
2	41	8.13	0.13–121.5	<1–11	0.4–0.6	
3	10	99.12	1.14–830.88	1–11	0.3–0.8	
4	1	3.42	3.42	1		
Total dose (ml)						
0.2	4	7.63	3.42–17.77	3–11		1
0.3	1	1.14	1.14	2		3
0.4	70	11.45	0.06–121.5	<1–12		1–2
0.6	12	83.31	1.14–830.88	1–11		2–3
0.8	2	6.84	3.42–10.26	1		3–3

The Leeds Overseas Travel Clinic have used the intradermal method for over 20 years, giving two injections of 0.1 ml HDCV, then repeating after an interval of at least 2 weeks (in practice usually four), or four injections of 0.1 ml at a single visit if time is limited. Intradermal immunisation offers a more cost effective use of rabies vaccine, which is both expensive and occasionally in limited supply. Cost effectiveness is a crucial factor in formulating advice and facilitating compliance for many budget travellers and for countries with limited health resources.

The study set out to explore the hypothesis that the antibody titres that result from intradermal immunisation decay over time, and that this is related to the dose of vaccine received.

2. Method

A retrospective cohort study design was selected as the basis for the study. Ethical approval was sought from the Leeds Research Ethics Committee. This was granted and the study given the Study number 06/Q1206/8 in spring 2006.

3. Subjects and recruitment

Through paper records held at the Leeds Overseas Travel Clinic approximately 300 people were identified whose most recent dose of intradermal pre-exposure rabies immunisation had been given between 1994 and 2005. From the record card details of the recorded address at the time of immunisation, date of birth, schedule of immunisation received and batches of vaccine used were obtained. For each year group approximately 30 records were identified. Until October 2004 only "Rabies Vaccine" (Sanofi Pasteur MSD) was used, thereafter some Rabipur vaccine (Novartis) was also brought into use.

Records were checked against the Exeter database for General Practitioner registrations. This permitted verification that the patient was still alive, and provided their current address. Patients were then invited to participate by postal invitation with a prepaid reply slip. Enrolment took place between September 2006 and January 2007. Positive responses were followed up with a telephone interview by a member of the research team. All participants gave written consent, confirmed their immunisation history, and were asked about any relevant medical history of immunosuppressive conditions or medications.

A sample size of 100, with 10 people immunised in each year from 1994 to 2004 had been sought. There were difficulties in recruitment, because people had moved away, changed names or did not wish to participate. Others who wished to participate had to be excluded for a variety of reasons, such as subsequent immunisation with intramuscular rabies vaccine, or concomitant immunosuppressive therapy.

4. Inclusion criteria

Patients receiving pre-exposure rabies prophylaxis from Leeds Overseas Travel Clinic between 1994 and 2005, with no subsequent rabies exposure or immunosuppression were included. Those patients who had received intramuscular rabies vaccine at any time were excluded from the study.

5. Outcome measures

At least 4 ml venous blood was taken from each eligible volunteer by a member of the study team. Serum was separated and refrigerated at Leeds Virology Department until all samples had been collected. All serum samples were tested by the fluorescent antibody virus neutralisation test [13] at the Veterinary Laboratories Agency, Weybridge. This test is regarded in the UK as the gold standard, with a high sensitivity for detecting antibody after immunisation. An antibody titre of greater than or equal to 0.5 IU/ml was considered indicative of seroconversion, providing an adequate titre, in line with World Health Organisation (WHO) recommendations [14]. The laboratory staff were blind to the immunisation history of each participant to reduce the risk of bias.