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Intradermal hepatitis B immunization with yeast-derived vaccine: serological response by sex and age

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SUMMARY

The efficacy and acceptability of yeast-derived recombinant hepatitis B vaccine given by the intradermal route was investigated in 221 health care volunteers. Two hundred and sixteen received a full course of three doses of vaccine. Only one subject was withdrawn because of a significant adverse reaction (psoriasis). The vaccine stimulated an antibody response in 81%. The response to the vaccine was better in women than in men (87% compared with 71%, $p = 0{\cdot}007$) and in women below the age of 40 years compared with older women (94% compared with 76%, $p = 0{\cdot}01$). For men the response showed a sequential decline with age for each decade (90% responders from age 29 or less, 72% aged 30–39 and 65% aged 40 or more, $p = 0{\cdot}04$). Retrospective enquiry showed that over 90% had found the intradermal route acceptable and 59% would prefer vaccine by the intradermal route in preference to intramuscular notwithstanding local reactions. Although the seroconversion rate was of a high order in younger women the antibody titres were not high with only 9 of 215 recipients developing titres > 1000 mIU/ml, a level which could be expected to ensure prolonged immunity. A fourth intradermal dose of vaccine given to 60 volunteers who had shown a low response (< 38 mIU/ml) or no serological response to a three-dose course stimulated a good booster effect (to 150–600 mIU/ml) in only 5 (8%).

INTRODUCTION

Careful evaluation of the intradermal (ID) route for hepatitis B immunization and of lower dose schedules has been advocated (1). Plasma-derived hepatitis B vaccine has been shown to promote an antibody response when given intradermally (2–4) ID vaccine has promoted satisfactory booster responses and may seroconvert some non-responders to earlier immunization (5). Lower seroconversion rates have been found to ID compared with intramuscular (IM) route (6–8) but the converse has also been observed (9). Although the geometric mean titre may be greater after IM (8), this difference may not necessarily be significant (10). The serological response has been greater in young adults than in older persons (11) but was less satisfactory in young children unless a jet-injection

method of application was used (12). The response to ID vaccine is improved by the presence of adjuvant (13). The persistence of antibodies in those immunized IM has been said to be greater than when ID immunization is used but others have found comparable persistence using ID (14) and the decline depends on an adequate initial antibody level. Intradermal vaccine is associated with more local reactions than IM (15) but these are typically minor and transient: delayed hypersensitivity reactions are dose related (16).

Although hepatitis B immunization is advocated for many health care workers its widespread use in the United Kingdom has been hampered by the high cost of the vaccine. The Joint Committee on Vaccination and Immunisation of the Department of Health and Social Security state (17) that the vaccine may be given by the intradermal route but on the doctor's personal responsibility until such a time as the manufacturers apply for and are granted variations to their product licences.

In the autumn of 1987 a yeast-derived recombinant DNA vaccine (Engerix B: Smith Kline & French, Welwyn Garden City.) became licensed in the United Kingdom for intramuscular application but it is not recommended by the manufacturers for intradermal use. The present study was undertaken to assess the validity of intradermal vaccination which, if successful and acceptable to vaccinees, could confer a substantial cost saving and thereby widen the population to whom prophylaxis can be offered.

PATIENTS AND METHODS

Health care staff in Shropshire working principally in surgery, midwifery and pathology were invited to volunteer for the study. Excluded from the study were those who had had one or more doses of hepatitis B vaccine or were currently undergoing alternative immunizations; current febrile illnesses; pregnancy or lactation; persons on immunosuppressive therapy or steroids; or a history of allergy or adverse reactions to previous vaccines. Volunteers were informed of the nature of the vaccine and that it was recommended for intra muscular use but for the present study it was being assessed by the intradermal route. They were warned that a proportion of recipients could be expected not to respond but were advised that in this event they would then be offered the vaccine by the intramuscular route after completion of the study. No prediction was made about the persistence of immunity. Warning was given on the adverse reactions which might be experienced, in particular local redness, soreness and induration at the injection site, depigmentation of negroid skin and possibly low-grade fever, malaise, fatigue, headache, nausea or dizziness.

Blood samples

Two hundred and twenty-one volunteers (all Caucasian men and women between 19 and 65 years old) were admitted to the study. All volunteers agreed to the collection of a blood sample before the first dose and a second sample 6–8 weeks after the third dose of vaccine.

Vaccination

The vaccine was administered intradermally into the flexor aspect of the forearm by the same operator (CAM). Each dose was 0·1 ml and contained 2·0 micrograms of protein comprising at least 95% hepatitis B surface antigen adsorbed on aluminum hydroxide as adjuvant together with Thiomersal 1:20000 as preservative. The hepatitis B surface antigen was produced by yeast cells using a recombinant DNA technique (Engerix B; Smith, Kline & French – batches 132 A4 and 143 A4.)

The course of vaccine required three intradermal inoculations, the first at time zero, the second 1 month later and the third 5 months after the second dose. Some non-responders and low responders were given a fourth dose of intradermal vaccine.

Adverse reactions

Volunteers were invited to report any adverse reaction and direct enquiry was made at the time of the next inoculation or blood sample collection. Local reactions were assessed by the same observer (CAM) and, on completion of the study, independently by a control of infection nurse.

Laboratory methods

Sera were collected at the Royal Shrewsbury Hospital and examined at the Public Health Laboratory, John Radcliffe Hospital, Oxford. The pre-vaccination specimens were tested for anti-HBs antibody using an enzyme immunoassay (Abbott Diagnostics Limited). Post vaccination specimens were titrated against the Blood Transfusion Service anti-HBs standard serum (12×10^3 mIU/ml) using a passive haemagglutination test (Serodia, Fujirebio Inc). Confirmation of non-reacting and low-titred sera in the latter test was done using the enzyme immunoassay.

RESULTS

Two hundred and sixteen of 221 volunteers completed the three dose course of immunization and provided post-immunization blood samples. One of these volunteers was shown to have been immune at the start of the study and was withdrawn from the assessment. Of the remaining five, one died of a subarachnoid haemorrhage (unrelated to the vaccine) during the course of the study; one was withdrawn after two doses of vaccine because of severe psoriasis (see below); one developed sciatica and transitory arthritis 2 months after the second dose of vaccine (presumed non-vaccine related) and declined the final dose; and two volunteers emigrated before final blood samples could be collected.

Adverse reactions to the vaccine

One patient was withdrawn from the study when she developed severe and acute urticaria followed by psoriasis with onset 10 days after the second dose of vaccine. This incident reminded her that she had experienced a similar exacerbation of psoriasis following natural measles many years before.

Sixty per cent of the patients developed a small (2–5 mm) red, painless but sometimes itching papule at the site of intradermal inoculation. Sometimes a more pronounced redness and induration appeared within 24–72 h of inoculation or was delayed until 7–21 days from the time of the injection and persisting from a few days to several weeks. Occasionally they were just discernable over several months. Several participants showed exacerbations or recurrence of the local reaction at earlier injection sites following a subsequent dose of vaccine. Local reactions were most common after the initial dose of vaccine but a smaller number of persons reacted to the second dose and three subjects showed substantial brisk local reddening and swelling to the third dose only, lasting up to 2 weeks. One individual experienced local cellulitis which resolved spontaneously, another experienced general malaise, headache and tightness of the chest for 24–72 h after the first and third dose of vaccine.

Serological response to three doses of vaccine

The serological response to the vaccine for men and women is shown in Table 1 and subdivided according to the age at the start of the immunization in Table 2. Statistical analyses were made using the chi-squared test with Yates' correction.

Seroconversion occurred in 118 of 136 women (87%) and 56 of 79 men (71%) showing a significantly better response by women than men ($p = 0{\cdot}007$). The response was better in women aged 39 or less (71 of 76; 93%) than in those aged 40 or greater (45 of 58; 78%, $p = 0{\cdot}02$). There was no significant difference in the response of women aged 20–29 and those aged 30–39 so that both groups have been combined for this analysis.

Not only did men respond less well than women but they also showed a progressive decline in responsiveness with each decade (24 of 29 men aged 29 or less compared with 20 of 28 and 12 of 22 in the age groups 30–39 and 40 years or greater, respectively; $p = 0{\cdot}04$).

The number of vaccinees who achieved titres of 100 mIU/ml or more was 38 of 78 (49%) females aged 39 years or less, 17 of 58 (29%) females aged 40 years or more, 4 of 29 (14%) males aged 29 years or less and 11 of 50 (22%) males aged 30 years or more.

Serological response to fourth dose of vaccine

Sixty volunteers who had shown no serological response to a course of three doses (10 women; 14 men) or a low serological response (< 38 mIU/ml; 22 women; 14 men) were given a fourth intradermal dose. A significant antibody rise ($\geqslant$ four-fold) was shown by 17 (28%) but a substantial antibody boost (within the range 150–600 mIU/ml) in only five (8%). Two of these were former non-responders and three were low responders.

Acceptability of the vaccine by the intradermal route

On completing their course of vaccine volunteers were asked if assuming efficacy of the vaccine, they would prefer intradermal (ID) or intramuscular (IM) vaccine. Over 90% of volunteers found the ID route acceptable with 59% preferring this route by choice. Less than 10% would have preferred IM injections.

Table 1. *Serological responses by volunteers given three doses of hepatitis B vaccine intradermally*

Post 3 dose ID Vaccine Antibody levels (mIU.ml)	Female		Male		Total	
	n	(%)	*n*	(%)	*n*	(%)
< 10	18	(13·2)	23	(29·1)	41	(19·1)
10	23	(16·9)	19	(24·1)	42	(19·5)
> 10 < 100	40	(29·4)	22	(27·8)	62	(28·8)
⩾ 100 < 1000	48	(35·3)	13	(16·5)	61	(28·3)
⩾ 1000	7	(5·2)	2	(2·5)	9	(4·2)
Serological response:						
No seroconversion	18	(13·2)	23	(29·1)	41	(19·1)
Seroconversion	118	(86·8)	56	(70·9)	174	(80·9)
Total population (*n*)	136		79		215	

Table 2. *Serological response by age and sex*

Antibody levels (mIU/ml)	Age (years)						
	19	20–29	30–39	40–49	50–59	⩾ 60	Total
				Female			
Neg	—	4	1	8	4	1	18
10	—	8	6	5	3	1	23
> 10 < 100	1	9	11	12	7	—	40
⩾ 100 < 1000	1	24	8	8	7	—	48
⩾ 1000	—	3	2	1	1	—	7
Total	2	48	28	34	22	2	136
				Male			
Neg	—	5	8	4	6	—	23
10	—	10	7	2	—	—	19
> 10 < 100	1	9	6	5	1	—	22
⩾ 100 < 1000	—	3	6	2	2	—	13
⩾ 1000	—	1	1	—	—	—	2
Total	1	28	28	13	9	—	79

Lack of correlation between seroresponse and local skin nodule formation

The serological response to the vaccine did not correlate with the development of a nodule at the site of injection. When the serological responses in those who developed a nodule were compared with those of a control group matched by sex and year of birth, no significant difference was found in the level of antibody in the two populations (paired *t*-test with 33 df; $t = 0{\cdot}47$; not significant). A local lesion therefore can not be relied upon to predict a satisfactory immune response to the vaccine.

DISCUSSION

The present study is unusual because it describes the response to a yeast derived-recombinant hepatitis B vaccine administered by the intradermal route to a wide age range of healthy males and females. The results indicate that although

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the ID route can be an economic alternative to intramuscular vaccine if given to younger health care workers (women under the age of 40 and perhaps men under the age of 30) a high proportion of vaccinees would require further immunization to provide prolonged immunity. Since only 8% of the non/low responders given a fourth dose of ID vaccine produced high levels of antibody we do not regard this additional procedure as routinely justified.

In this study > 100 mIU/ml has been judged as a satisfactory level of immunity expected to provide protection for 2 years or longer. However, in other studies 1000 mIU/ml has been demonstrated in a greater proportion of persons receiving three intramuscular doses of vaccine and in these protection can be expected to persist for 4–5 years; such antibody levels were only achieved in our own intradermal study by 9 of 215 volunteers.

Since vaccine given IM or ID is associated with a failure in serological response in some individuals, post immunization serological checks are essential, at least in an occupational health service, to identify non-responders or low responders (< 100 mIU/ml). Periodic checks for persistence of immunity may also be required.

The better response of women compared with men and the age relationship is highly relevant because the majority of health care workers demanding immunization are women in the younger age groups. The sex difference which we observed is consistent with the observations in a study of 30 volunteers in Germany (18), in which the response to the first two doses of recombinant hepatitis B vaccine given IM was poorer in younger men than in young women. Possible explanations for the better response of women to the ID route may be the increased vascularity of female skin in response to oestrogens, and oestrogen stimulation of the reticulo-endothelial system including the Langhans giant cells of the skin (19). The role of female sex hormones in increasing the immune response to bacterial and viral infections, including hepatitis B has previously been suggested and discussed (20).

The intradermal route proved highly acceptable to the recipients and was generally preferred to intramuscular injection. With the exception of one volunteer who experienced an exacerbation of psoriasis (a rare complication which has also been recorded with serum derived vaccine (21)), the vaccine induced no significant reactions. Sixty per cent of those immunized showed a small local macule or papule at one or more inoculation sites, sometimes persisting for 2 months or more and comparable to a tuberculin response; none found this unacceptable. The local reaction correlated poorly with the antibody response; it was probably a reaction to the aluminium hydroxide component of the vaccine. Transient episodes of acute arthropathy have been described as adverse reactions to plasma-derived hepatitis B vaccine (22, 23) and yeast-derived vaccine (24). These episodes differ from the incident of late onset sciatica followed by polyarthralgia experienced by one of our subjects who had an episode which we consider was unlikely to have been vaccine-associated because of the nature of the illness, time relationship to the vaccine and age of the patient.

We suggest that where intradermal hepatitis B immunization is being considered as an economic alternative to intramuscular vaccine for health care workers, it is likely to be most suitable for women under the age of 40. However, for most of those given the yeast-derived recombinant vaccine intradermally, the

antibody titres achieved will be inadequate to ensure prolonged immunity (5 years) and in the Occupational Health context, particularly in more affluent countries, the intramuscular route is to be preferred.

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