Immunogenicity of standard and low dose vaccination using yeast-derived recombinant hepatitis B surface antigen in elderly volunteers

S. de Rave*‡, R.A. Heijtink†, M. Bakker-Bendik*, J. Boot* and S.W. Schalm*

There is no conclusive evidence that age influences the response to vaccination against hepatitis B virus. We therefore studied the immunogenicity of yeast-derived rHBsAg vaccine in elderly volunteers. The study was conducted in the outpatient clinics of an academic and a regional hospital, in a rural family practice and in an urban community centre. We recruited 112 healthy volunteers aged 59 years and over, to whom 10 or 20 μg yeast-derived HBsAg was given at 0, 1 and 6 months. Anti-HBs titres were measured by radioimmunoassay at 2, 6 and 7 months. Responders and non-responders were compared using univariate non-parametric tests and multivariate logistic regression analysis. Of the 116 subjects who volunteered to take part in the study, 106 vaccinees completed it. The percentage of subjects with an anti-HBs titre $\geqslant 10\ IU\ l^{-1}$ *at 7 months was 60% (95% confidence interval: 51–70%; geometric mean titre: 253* $IU\ l^{-1}$*). Of the factors studied, i.e. setting, age, sex, alcohol consumption, current medication and vaccine dose, the use of medication at the time of the first vaccination was the only independent factor related to the response to vaccination, with a response rate of 78% (95% confidence interval: 66–89%) in those without medication. In elderly subjects, the proportion with protective concentrations of anti-HBs after vaccination with 10 or 20 μg yeast-derived recombinant HBsAg in a standard scheme is lower than in healthy adolescents. Within the older age group studied here, the use of medication, probably reflecting general health, is the only significant factor influencing the response to vaccination.*

Keywords: Hepatitis B vaccination; rHBsAg; immunogenicity; elderly subjects

The development of plasma-derived hepatitis B virus (HBV) vaccines, succeeded by safe and efficacious recombinant HBsAg vaccines[1], has opened the way to mass vaccination against hepatitis B. Most candidates for hepatitis B vaccination are either infants or young adults. However, hepatitis B vaccination is also indicated for elderly subjects in high-risk groups. Among the risk factors are admission to chronic care facilities, chronic haemodialysis and visits to endemic areas. Some elderly health care workers also require hepatitis B vaccination. There are suggestions but no definite proof that the response to vaccination declines with advancing age, as has been described for the influenza virus[2]. A negative effect of age on the response to hepatitis B vaccination in healthy volunteers[3,4], patients with Down's syndrome[5] and patients on chronic haemodialysis[6,7] has been reported. Plasma-derived vaccines were used in these studies. It is not clear whether there are other negative influences or whether the possible negative effect of age can be overcome, for instance by the use of recombinant HBsAg vaccine or by increasing the dose of hepatitis B vaccine. We therefore compared the effect of 10 μg and 20 μg yeast-derived recombinant HBsAg in a standard schedule with vaccinations at 0, 1 and 6 months in 112 healthy elderly volunteers. The dose of 20 μg is recommended and is probably above optimal in healthy adolescents[1]. A dose of 10 μg was used for comparison because the effect of other factors, such as age and general health, were expected to be more readily discernible at this dose.

PATIENTS AND METHODS

A total of 116 healthy volunteers aged 59 years and older were screened for inclusion in the study. Healthy was defined as being self-supporting and free of life-threatening disease. The number of men was 65.

*Department of Internal Medicine II and †Department of Virology, University Hospital Dijkzigt, Erasmus University, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. ‡To whom correspondence should be addressed. (Received 21 January 1993; revised 29 July 1993; accepted 9 August 1993)

0264-410X/94/06/0532–03
© 1994 Butterworth-Heinemann Ltd

Table 1 Indications for and types of medication in volunteers participating in the study on the immunogenicity of yeast-derived recombinant HBsAg in elderly subjects

Disorder	Medication	Number of patients
Cardiovascular	Diuretics	15
	Aspirin	9
	Calcium entry blockers	8
	ACE inhibitors	8
	β-adrenoreceptor blockers	5
	Others	8
Gastrointestinal	Antacids	13
	5-ASA	4
	Others	7
Asthmatic	Topical	6
	Systemic	2
Endocrine	Thyroid hormone	6
	Anti-thyroid	3
	Oral antidiabetic	7
	Insulin	4
Miscellaneous	Vitamins/iron/folic acid	7
	Analgesics/NSAIDs	5
	Others	17
Total		134

Note: Some patients used more than one prescription from the same category

Exclusion criteria were the use of immunosuppressant drugs or anticoagulants. Informed consent was obtained in all cases. The study was conducted between February 1989 and February 1992. Subjects were recruited in the outpatient clinics of an academic hospital and of a regional hospital, in rural family practice and in an urban community centre. The use of medication and alcohol was recorded. No medication was used by 51 patients, while the remaining 61 used 151 prescriptions (*Table 1*). The study was approved by the ethical committees of the participating centres. Of the 116 volunteers screened, three men and one woman were anti-HBs- and anti-HBc-positive, and these four were excluded. The remaining 112 volunteers were included in the study. Participants were randomized by order of entry in fixed blocks of six. A vaccine dose of 10 μg (scheme A) yeast-derived recombinant HBsAg (Engerix-B) was given to 56 subjects and a dose of 20 μg (scheme B) was given to the remaining 56 by intramuscular injection in the deltoid region. There were no significant differences between groups with regard to age, sex, setting, daily amount of alcohol consumed or number of current prescriptions. Injections were given at 0, 1 and 6 months. Blood was drawn from an antecubital vein for anti-HBs measurement by radioimmunoassay (Ausab, Abbott Laboratories, Chicago, IL, USA; using a WHO standard) at 2, 6 and 7 months. Five persons withdrew before completion of the study, three in scheme A and two in scheme B, one because of a rise in his insulin requirement and the others for non-medical reasons. No other side-effects of vaccination were noted. Three anti-HBs titres at 2 months are missing in the remaining 107 patients, two in scheme A and one in scheme B. By interpolation, the two missing values in scheme A can be assumed to equal zero. No anti-HBs titre at 7 months is available for one patient in scheme A. In the statistical analysis, actuarial (Kaplan–Meier) response rates for the total group of 112 participants and absolute response rates for the 106 subjects who had anti-HBs measured at 7 months were almost identical. In this report, only absolute numbers will be considered. Non-parametric tests (Fisher and Mann– Whitney) were used for the comparison of groups. Logistic regression analysis was used for multivariate testing of the effects on response rate. In a study of 112 patients at $\alpha = 0.05$ and $\beta = 0.10$, differences of $< 30\%$ between two groups may go undetected.

RESULTS

An anti-HBs titre $\geqslant 10\,IU\,l^{-1}$ at 7 months was found in 30 out of 52 subjects in scheme A (58%, 95% confidence interval (CI): 45–71%) and in 34 out of 54 in scheme B (63%, 95% CI: 50–76%). At two months, these figures were 12 and 9%, respectively, and at 6 months they were 27 and 24%, respectively (*Figure 1*). These differences between scheme A and scheme B are not significant ($p > 0.05$, Fisher test). The anti-HBs titres in responders ($\geqslant 10\,IU\,l^{-1}$) at 2, 6 and 7 months (*Table 2*) also fail to show significant differences between scheme A and scheme B ($p > 0.05$, Mann–Whitney test), The geometric mean titre at 7 months was $253\,IU\,l^{-1}$ for the total group.

Univariate testing of differences between responders and non-responders (*Table 3*) yielded no significance for sex, vaccine dose, daily amount of alcohol consumed or age. Significant differences were found for the setting of the vaccination trial (in or out of hospital, $p = 0.049$) and for the use of medication at the time of the first vaccination ($p = 0.001$). Multivariate logistic regression analysis shows that the use of medication at the time of

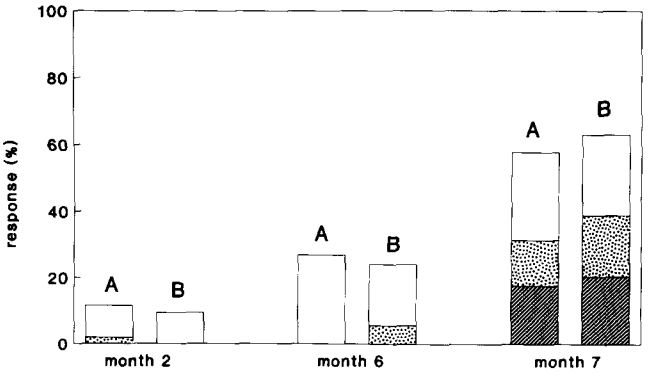

Figure 1 Response to vaccination with (A) 10 μg or (B) 20 μg yeast-derived recombinant HBsAg in elderly volunteers at different times: (▨) anti-HBs $> 1000\,IU\,l^{-1}$; (▩) anti-HBs $> 100\,IU\,l^{-1}$; (□) anti-HBs $> 10\,IU\,l^{-1}$

Table 2 Anti-HBs titres in responders (anti-HBs $\geqslant 10\,IU\,l^{-1}$) to vaccination with 10 or 20 μg yeast-derived recombinant HBsAg at different times after first vaccination

Months after first vaccination	Vaccine dose	Number of responders	Anti-HBs geometric mean titre ($IU\,l^{-1}$)	Anti-HBs range ($IU\,l^{-1}$)	p^a
2	10	6	35	11–473	0.58
	20	5	20	10–65	
6	10	14	30	13–93	0.72
	20	13	33	10–131	
7	10	30	203	10–6720	0.44
	20	34	308	12–13 736	

[a]Mann–Whitney test

Table 3 Comparison of entry characteristics in responders (anti-HBs $\geqslant 10\,IU\,l^{-1}$) and non-responders to vaccination with yeast-derived recombinant HBsAg using univariate tests

	Responders	Non-responders	*p*
Sex (male/female)	36/28	24/18	1.00[a]
Vaccine dose (10 μg/20 μg)	30/34	22/20	0.69[a]
Alcohol (ml day^{-1}: median, range)	0, 0–10	0, 0–20	0.37[a]
Age (years: median, range)	67, 61–79	68, 59–81	0.31[b]
In/out of hospital	42/22	35/7	0.049[a]
Medication (yes/no)	26/38	31/11	0.001[a]

[a]Fisher test
[b]Mann–Whitney test

the first vaccination is the only independent factor related to presence or absence of an anti-HBs response $\geqslant 10\,IU\,l^{-1}$ after 7 months ($p=0.001$).

DISCUSSION

The present study clearly shows that the response rate in elderly volunteers vaccinated with yeast-derived rHBsAg (60%, 95% CI: 51–70%) was below that expected for healthy adolescents. For 870 healthy volunteers below the age of 40 years, a response rate of 99.5% (95% CI: 99.1–100%) has been reported after a vaccination course identical to that in our study[1]. In a study in 141 newborns[8] conducted at the same time with the same vaccine, a 100% response to vaccination was found, which makes technical flaws related to the vaccine or to the antibody measurements an unlikely reason for our finding of low responsiveness.

Contrary to our expectations, we found no differences between the 10 μg and the 20 μg doses. The only factor with a negative influence on the response rate in our study was the use of medication at the time of the first vaccination. The response rate was 78% (95% CI: 66–89%) in the group without medication compared with 46% (95% CI: 33–59%) in the group using one or more prescriptions. The use of medication may reflect poorer general health in the latter group. Even in the subjects without medication, the response rate was below that reported for younger age groups. Within the group studied here, we found no relationship between age and response to vaccination, contrary to the report by Denis *et al.*[3]. Their study does not mention the use of medication by the vaccinees, which may be an alternative explanation for the difference found between their age categories.

In conclusion, age appears to be a very important factor in the immune response to recombinant HBsAg, even though our study did not include a younger control group. Within the group of elderly volunteers, the response to vaccination with yeast-derived recombinant HBsAg is further influenced by general health as reflected by the use of medication.

ACKNOWLEDGEMENTS

The authors are grateful to J. Geldof, G.H. de Groot and J.W. den Ouden-Muller for their help in recruiting volunteers and W.C.J. Hop for his statistical advice. This study was designed in close cooperation with Dr A. Safary and supported by a grant from SmithKline Beecham Pharmaceuticals.

REFERENCES

1 André, F.E. Summary of safety and efficacy data on a yeast-derived hepatitis B vaccine. *Am. J. Med.* 1989, **87**(Suppl. 3A), 14S–20S
2 Beyer, W.E.P., Palache, A.M., Baljet, M. and Masurel, N. Antibody induction by influenza vaccines in the elderly: a review of the literature. *Vaccine* 1989, **7**, 385–395
3 Denis, F., Mounier, M., Hessel, L., Michel, J.P., Gualde, N., Dubois, F. *et al.* Hepatitis B vaccination in the elderly. Letter. *J. Infect. Dis.* 1984, **149**, 1019
4 Morris, C.A., Oliver, P.R., Reynolds, F. and Selkon, J.B. Intradermal hepatitis B vaccination with yeast-derived vaccine: serological response by sex and age. *Epidemiol. Infect.* 1989, **103**, 387–394
5 Troisi, C.L., Heiberg, D.A. and Hollinger, F.B. Normal immune response to hepatitis B vaccine in patients with Down's syndrome. *JAMA* 1985, **254**, 3196–3199
6 Smit-Leijs, M.B.L., Kramer, P., Heijtink, R.A., Hop, W.C.J. and Schalm, S.W. Hepatitis B vaccination of haemodialysis patients: randomized controlled trial comparing plasma-derived vaccine with and without pre-S_2 antigen. *Eur. J. Clin. Invest.* 1990, **20**, 540–545
7 Bruguera, M., Rodicio, J.C., Alcazar, J.M., Oliver, A., Del Rio, G. and Esteban-Mur, R. Effects of different dose levels and vaccination schemes on immune response to a recombinant hepatitis B vaccine in haemodialysis patients. *Vaccine* 1990, **8**(Suppl.), S47–49
8 del Canho, R., Grosheide, P.M., Voogd-Schotanus, M., Huisman, P.M., Heijtink, R.A. and Schalm, S.W. Immunogenicity of a full dose (20 μg) of recombinant DNA hepatitis B vaccine in healthy neonates: A comparison of three different vaccination schemes. *J. Med. Virol.* 1993, **41**, 30–34