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Immunogenicity of yeast-derived hepatitis B vaccine from two different producers

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SUMMARY

The immunogenicity and reactogenicity of two preparations of yeast-derived hepatitis B vaccines were compared in healthy adult populations. The two groups were vaccinated in parallel, but they were not matched for age and sex. All subjects seroconverted, and 9 months after the first vaccine dose, all had anti HBs titres of at least 10 IU/l. The anti-HBs titres were higher in the group of subjects given 20 μg vaccine antigen made by Smith Kline & RIT (GMT 2943 at 9 months) compared to those who received 10 μg of vaccine made by Merck, Sharp & Dohme (GMT 729 at 9 months). Adverse effects were recorded in 32·0 and 44·7% of the participants, but these were limited to minor local and general reactions. In the present study both preparations were safe and efficient.

INTRODUCTION

Plasma-derived hepatitis B vaccine, containing purified and inactivated HBs antigen from chronic carriers, has been commercially available since 1982. This vaccine has been widely used all over the world with considerable success. It has proved to be highly effective in preventing infection, especially in healthy individuals with a minimum of side effects [1]. Non-responsiveness to the vaccine is more prevalent in individuals with some degree of immunodeficiency, but even this problem can often be overcome by increasing the dose. Nevertheless, in spite of an overwhelmingly positive general impression, the high cost of production and the unfounded reservations about its safety have limited acceptance of the vaccine by many individuals at risk. Development of yeast-derived vaccines, based on recombinant DNA technology [2, 3], can to a large extent eliminate arguments against safety, increase the level of production to match needs and gradually reduce production costs.

In the present study we have tested the immunogenicity and the incidence of undesirable reactions to the two available yeast-derived vaccines in hospital-employed healthy volunteers.

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Table 1. *Age and sex distribution of the participants*

Vaccine preparation	Total no.	Mean age	(Range)	Male		Female	
				n	Mean age	*n*	Mean age
SKR 20 μg	69	31	(22–62)	15	37	54	27
MSD 10 μg	70	24	(21–53)	15	28	55	23

MATERIALS AND METHODS

Subjects

One hundred and forty volunteer employees at the National Hospital were selected for the study. They were all negative for hepatitis B virus (HBV) parameters: HBsAg, anti-HBs and anti-HBc, had normal ASAT and ALAT levels and had not previously received any form of hepatitis vaccine. Persons with known allergies and pregnant women were excluded from the study. All gave informed written consent prior to inclusion in the study. Seventy consecutive persons were vaccinated with the SKR vaccine first because it became available earlier, followed by 70 consecutive persons vaccinated with the MSD vaccine. No attempt was made to match the two groups. The age and sex distribution of the two groups is shown in Table 1.

Vaccines

Hepatitis B vaccines Engerix B (Smith Kline – RIT, 20 μg Batch: 8GPh) and Recombinant (Merck Sharp & Dohme, 10 μg, Lot 978/C-K563) were used. The vaccines were stored at 4 °C until used.

Procedure

The participants were injected intramuscularly into the deltoid region with 1 ml of the vaccine at 0, 1 and 6 months. All injections were given by the same person. The participants were asked to record their temperatures and any local or systemic reactions for 5 days after each inoculation. Blood samples were obtained at 0, 1, 3, 6 and 9 months after the first dose of the vaccine. The sera were separated and kept at −20 °C.

Test procedures

Each of the test series for anti-HBs contained equal numbers of comparable specimens from both vaccine groups. All serum samples obtained during the study were tested for HBsAg by Ausria II, anti-HBs by Ausab RIA (Abbott Laboratories, N. Chicago, IL.) and ASAT and ALAT. The initial and the last samples from each participant was also tested for anti-HBc by Corab (Abbott Laboratories). The anti-HBs titres were expressed in International Units per litre (IU/l). The serological tests were performed blind.

Statistical analysis

The data were analysed by Student's t test, the χ^2 test and the Mann–Whitney test. P values of 0·01 or less were considered to be significant.

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Table 2. *Seroconversion rates (%) for two yeast-derived vaccines at different times after the first dose*

Vaccine preparation	Time after the first dose (months)			
	1	3	6	9
SKR 20 μg	30	97	100	100
MSD 10 μg	33	97	100	100

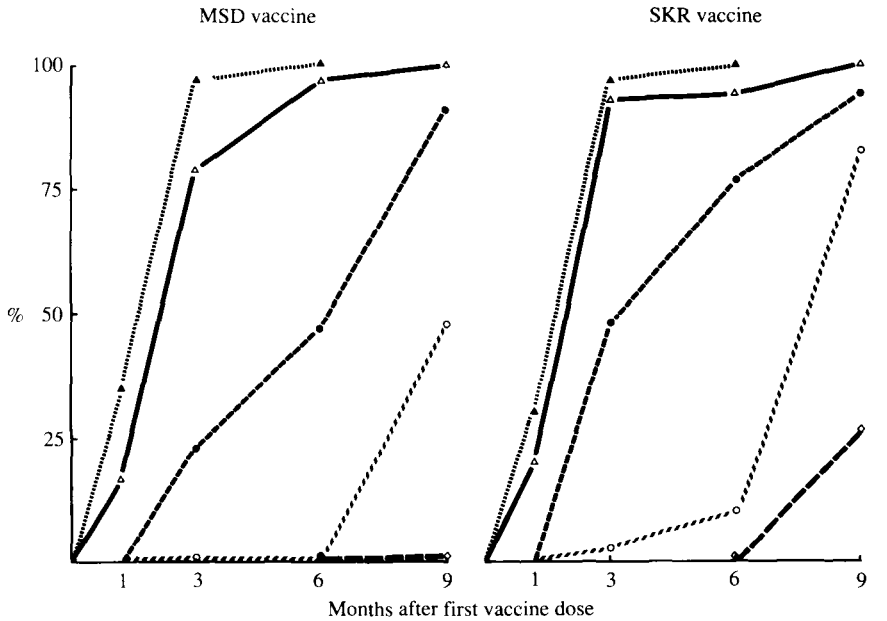

Fig. 1. Development of antibodies against HBsAg in healthy adults who received three doses of yeast derived hepatitis vaccines from two different producers. (▲...▲, > 1; △—△, > 10; ●----●, > 100; ○----○, > 1000; ◇----◇, > 10000 IU/l)

RESULTS

All participants in both groups had a positive immune response to the vaccines. One participant in the SKR group could not be evaluated because of insufficient number of blood samples. The seroconversion rates (anti-HBs > 1 IU/l), shown in Table 2, increased rapidly to about 30% at 1 month, 97% at 3 months and 100% at 6 months after the start of the programme. The rates for seroconversion was practically identical in the two groups.

A quantitative analysis of the immune response is illustrated in Fig. 1. At the end of the observation period all participants had anti-HBs in excess of 10 IU/l. However, the group that received the SKR vaccine had significantly higher titres at 3, 6 and 9 months. This is further illustrated by the data shown in Table 3. The median titres were significantly higher in the SKR group at each time. At 9 months one vaccinee in the MSD group had antibody titres 10000 or higher and

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Table 3. *Differences in anti-HBs titres between the participants given different vaccine preparations at different times after the first dose*

Vaccine preparation	Time after the first dose (months)	
	6	9
SKR 20 μg	189*	2943
MSD 10 μg	99	729

* IU/litre, geometric mean.

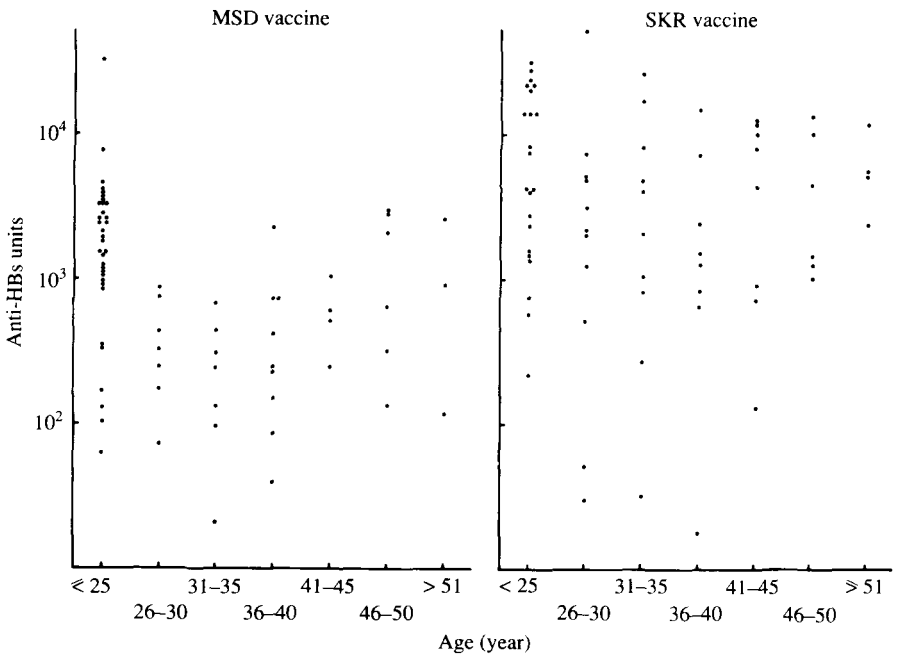

Fig. 2. Antibody response against HBsAg in various age groups of healthy adults to three doses of two different products of yeast-derived hepatitis B vaccines, 9 months after the initial dose.

31 had 1000 or more. The corresponding numbers in the SKR group were 19 and 54. These differences are also highly significant. The titres were higher both among female and male participants and the antibody titres were significantly higher in females than in males in both groups.

The antibody titres distributed in various age groups are illustrated in Fig. 2. There is a tendency towards higher titres in the youngest group of participants with both vaccines. Participants born before 1960 had significanty higher titres than those born after 1960.

All tests for HBsAg and for anti-HBc were negative in both groups.

Adverse effects were noted by the participants during the first 5 days following each injection, although these were not confirmed by a physician. In all, side

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Table 4. *Frequency of side effects in two groups of vaccinees given either* 20 μg of SKR or 10 μg *of MSD vaccine*

	Side effects							
	SKR vaccine				MSD vaccine			
	No.*	Local	General	No symptoms	No.	Local	General	No. symptoms
1	70	8	39	41	70	25	35	31
2	68	8	27	47	69	17	18	39
3	65	6	13	50	58	15	10	39

*Number of symptom sheets returned.

effects were noted in 32·0% and 44·7% of vaccines in the SKR and the MSD groups respectively, and these are summarized in Table 4. Most of the complaints were mild soreness at the injection site with moderate general symptoms, frequently fever, and most often on the day of vaccination or day after. No serious or incapacitating symptoms were recorded and none of the vaccinees declined second or third doses of vaccine because of side effects. Slight elevation of ASAT and ALAT levels developing during the vaccination period was seen in 4 out of 70 participants receiving the SKR vaccine and in 13 out of 70 receiving the MSD vaccine. In all these cases the values became normal or slightly but insignificantly elevated during the follow-up period.

Two participants, one in each vaccination group, had slightly elevated transaminase levels before receiving the first dose of vaccine. One of these had a history of previous non A, non-B hepatitis. Both participants continued to have abnormal transaminase levels during the follow-up period.

All in all the total number of side effects was somewhat higher in the MSD group, but were equally mild with both vaccines.

DISCUSSION

The main conclusion of this study is that both preparations of yeast-derived hepatitis B vaccines are safe and effective for use in healthy adults. The rate of seroconversion was 100% with both vaccines and the kinetics of seroconversion were comparable. The results were similar to those published previously with the plasma-derived vaccines, and the results reported from other trials with the yeast derived vaccines [5–7]. However, it should be remembered that some reports have indicated that the immune response to recombinant vaccines may be slower and lower compared with the plasma-derived vaccine [4,8].

In the present study those participants given the SKR vaccine produced higher levels of antibody than the MSD preparation. It is possible that the reason for this difference is that the two vaccines do not contain the same amount of antigen in each dose [4]. One dose of the SKR vaccine contains 20 μg compared with 10 μg in the MSD vaccine. None the less in another recently published study [9] 2 μg of MSD recombinant DNA vaccine induced higher antibody levels in children than the same dose of recombinant DNA vaccine from SKR. The two groups of

participants in the present investigation were comparable with respect to sex-distribution and the age distribution should rather favour the MSD group with a higher proportion of younger individuals. It is, however, necessary to remember that the two groups were not randomly selected. Whether the slight difference in antibody levels obtained is of practical importance is unknown. It is usual to consider anti-HBs plasma levels of 10 IU/l to have a protective effect [10, 11]. In our groups all participants developed antibody levels greater than 10 IU/l.

Experience with the plasma-derived vaccine shows that the antibody levels tend to decline with time and that revaccination with a booster dose may be necessary [12, 13]. There is no reason to believe that it will be different with yeast-derived vaccines. Indeed, one recent prelimary report has suggested a more rapid loss of protective antibodies after recombinant vaccine than after plasma derived vaccine [14]. Whether the slightly higher levels of antibodies produced with the 20 μg dose of SKR vaccine will last longer than those following the 10 μg doses of MSD vaccine remains to be seen.

Neither vaccine contains the antigen coded for by the pre-S gene. It has been suggested [15] that this antigen could enhance the protection afforded by the vaccine. The question is still open but the two vaccines used in the present study are comparable in this respect.

No serious adverse effects were observed in the participants. The self-recorded complaints were limited to mild local and general symptoms, and none of our subjects objected to receiving the remaining injections of vaccine. The overall frequency of the complaints may seem to be higher than in similar trials elsewhere. One possible explanation may be that all the participants were instructed to record all symptoms thoroughly and this instruction may have encouraged the participants to be more than usually observant. Also the participants were health personnel possibly with a higher awareness of minor symptoms and signs than the non-medical vaccinees.

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