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Immune Responses to Late Booster Doses of Hepatitis B Vaccine

Wolfgang Jilg, Marion Schmidt, and Friedrich Deinhardt

Max von Pettenkofer Institute, University of Munich, Pettenkoferstr. 9a, D-8000 Munich 2

Nineteen healthy young adults were vaccinated with plasma-derived hepatitis B vaccine at months 0, 1, and 12, and their immune responses were compared to those of a similar group of 20 vaccinees immunized at months 0, 1, and 6. Late booster injections at 12 months produced nearly fivefold higher geometric mean anti-HBs levels than those of the control group. The higher anti-HBs values may lead to longer persistence of anti-HBs and thus to longer protection against hepatitis B.

Key words: hepatitis B vaccine, immune responses, vaccination schedules

INTRODUCTION

Vaccination against hepatitis B is currently the most important means of preventing this disease, and the vaccines that have been used in one to two million individuals are highly immunogenic, effective, and safe [Stevens et al, 1984; Shaw et al, 1984]. However, as with most other inactivated vaccines, after a course of immunization against hepatitis B, antibodies decline rather rapidly [Hadler et al, 1984; Zachoval et al, 1984]. Earlier studies indicated that revaccination after five years was sufficient to maintain the antibody levels to hepatitis B surface antigen (anti-HBs) above 10 IU/l, which is considered to be the minimal protective level [Goudeau et al, 1982; Szmuness et al, 1981], but long-term trials have shown that in a considerable number of vaccinees anti-HBs concentrations fell below this level or even disappeared much earlier [Hadler et al, 1984; Jilg et al, 1984]. Recently, a close correlation was demonstrated between the peak anti-HBs concentration after the basic immunization and the persistence of specific antibodies [Jilg et al, 1984; Laplanche et al, 1984; Grob et al, 1985]; vaccination strategies should therefore aim at the highest possible initial anti-HBs concentration, as this may ensure long-term persistence of anti-HBs and protection against hepatitis B. The anti-HBs response depends on the immunogenicity of the vaccine, but it may also be influenced by the timing of the injections during the first course of immunization. From studies with the vaccine

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Address reprint requests to Dr. W. Jilg, Max von Pettenkofer Institute, Pettenkoferstr. 9a, D-8000 Munich 2, Federal Republic of Germany.

manufactured by the Institut Pasteur Production, in which the booster injection was given 12 months after the first vaccination, there is some evidence that a late booster results in higher anti-HBs concentrations than a booster given at 6 months as recommended for the Merck, Sharp, and Dohme vaccine [Goudeau et al, 1982; Laplanche et al, 1982; Szmuness et al, 1981; Zachoval et al, 1984]. In the study reported here, we examined the effect of a late booster dose on the anti-HBs response by comparing anti-HBs concentrations in a group of vaccinees immunized three times with the Merck vaccine at months 0, 1, and 12 with an age- and sex-matched control group vaccinated according to the usual schedule (injections at 0, 1, and 6 months).

MATERIALS AND METHODS

Study Population

Participants were 39 healthy young adults, mainly medical students, who were negative for hepatitis B surface antigen (HBsAg), anti-HBs, and antibodies against hepatitis core antigen (anti-HBc). They were divided into two groups (group I, study group; group II, control group); the sex and age distributions are shown in Table I.

TABLE I. Sex and Age Distribution of the Two Vaccination Groups

	Female		Male		Total	
	No.	Age (years)[a]	No.	Age (years)[a]	No.	Age (years)[a]
Group I (Late booster)	8	22.0 ± 4.0 (17–30)	11	24.6 ± 2.6 (18–28)	19	23.4 ± 3.5 (17–30)
Group II (Control)	9	22.4 ± 3.0 (18–27)	11	25.3 ± 2.5 (21–30)	20	24.0 ± 3.0 (18–30)

[a]Arithmetic means and standard deviations (range).

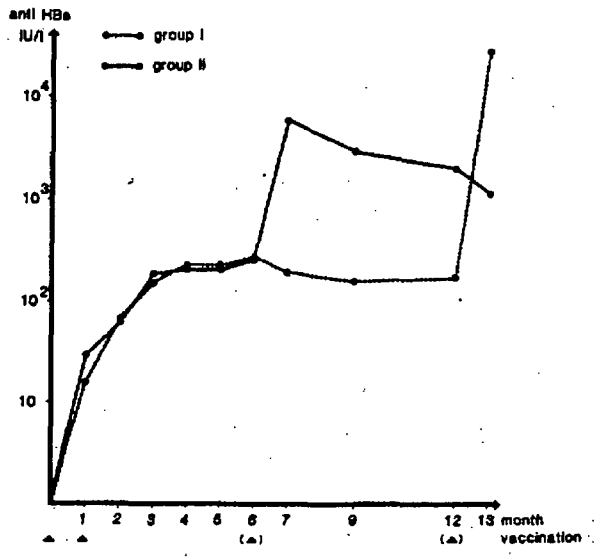

Fig. 1. Anti-HBs concentrations (geometric means) in group I (booster injection at month 12) and group II (booster injection at month 6) during vaccination.

Vaccine and Vaccination Schedules

Hepatitis B vaccine consisting of purified HBsAg, 20 μg per dose (HB-Vax), was kindly supplied by Merck, Sharp, and Dohme, Munich, Federal Republic of Germany. Group I participants received three doses of vaccine at months 0, 1, and 12; vaccinees of the control group (group II) were injected at months 0, 1, and 6 (regular schedule). Injections were given intramuscularly in the upper arm. Blood was taken monthly for seven months, and thereafter at months 9, 12, and 13.

Determination of HBsAg, Anti-HBs, and Anti-HBc

HBsAg, anti-HBs, and anti-HBc were tested using commercially available radioimmunoassays (AUSRIA II, AUSAB, CORAB, Abbott Laboratories, Chicago, IL). Anti-HBs concentrations were calculated according to Hollinger [Hollinger et al, 1982] using the International Reference Standard [WHO, 1979] at a dilution of 1:400. Statistical analysis was done by Student's t-test.

RESULTS

The immune response to two doses of vaccine given at month 0 and 1 was similar in both groups; no differences in geometric mean anti-HBs concentrations were seen in the two groups during the first 6 months. At 6 months, this value was 283 IU/l in group I and 266 IU/l in group II; seroconversion was 100% in both groups. The booster injection in group II, given at month 6, increased the anti-HBs to a geometric mean anti-HBs concentration of 6,235 IU/l at month 7, which decreased to 1,196 IU/l during the next six months. In group I, anti-HBs concentration declined slightly between month 6 and 12 from 283 IU/l to 185 IU/l, and the booster dose at month 12 in this group produced a dramatic rise in anti-HBs to a geometric mean concentration of 31,107 IU/l. Thus, in group I geometric mean anti-HBs concentration four weeks after the final (booster) dose of hepatitis B vaccine was nearly five times higher than in the regularly vaccinated group II, a highly significant finding ($p < 0.005$) (Table II, Fig. 1).

TABLE II. Immune Response During the Course of Vaccination

	Group I (late booster)			Group II (control)		
Month	Sero conversion (%)	Log anti-HBs[a] (mean + SD)	Anti-Hbs[a] (geometric mean) IU/l	Sero conversion (%)	Log anti-Hbs[a] (mean + SD)	Anti-Hbs[a] (geometric mean) IU/l
1	52	1.22 ± 0.37	16	60	1.49 ± 0.82	31
2	100	1.85 ± 0.51	70	82	1.81 ± 0.66	65
3	100	2.19 ± 0.43	154	89	2.29 ± 0.72	194
4	100	2.42 ± 0.25	263	100	2.32 ± 0.83	208
5	100	2.42 ± 0.18	263	100	2.31 ± 0.70	205
6	100	2.45 ± 0.44	283	100	2.42 ± 0.71	266
7	100	2.30 ± 0.42	201	100	3.80 ± 0.86	6,235[b]
9	100	2.23 ± 0.41	169	100	3.49 ± 0.77	3,069
12	100	2.27 ± 0.38	184	100	3.33 ± 0.79	2,132
13	100	4.49 ± 0.24	31,107[b]	100	3.08 ± 0.88	1,196

[a]Responders only.
[b]One month after booster injection.

After the booster in group II, five individuals (25%) had anti-HBs values below 1,000 IU/l, whereas all vaccinees of group I had values above 1,000 IU/l (lowest value 2025 IU/l) after the third immunization. The highest concentration in the control group was 75,980 IU/l, whereas in group I, five individuals (26%) showed higher values with a maximum level of 288,370 IU/l in an 18-year-old male. The individual responses to the booster injections in the 39 participants of the two groups are shown in Figure 2.

None of the participants in group I and II developed HBsAg or anti-HBc.

DISCUSSION

In this study, an immunization schedule with a late booster injection at month 12 resulted in a nearly fivefold higher geometric mean anti-HBs concentration than that in the control group. To our knowledge, such anti-HBs concentrations have not been observed previously in studies with the Merck vaccine, although similar values were reported from trials with the Pasteur vaccine [Goudeau et al, 1982; Laplanche

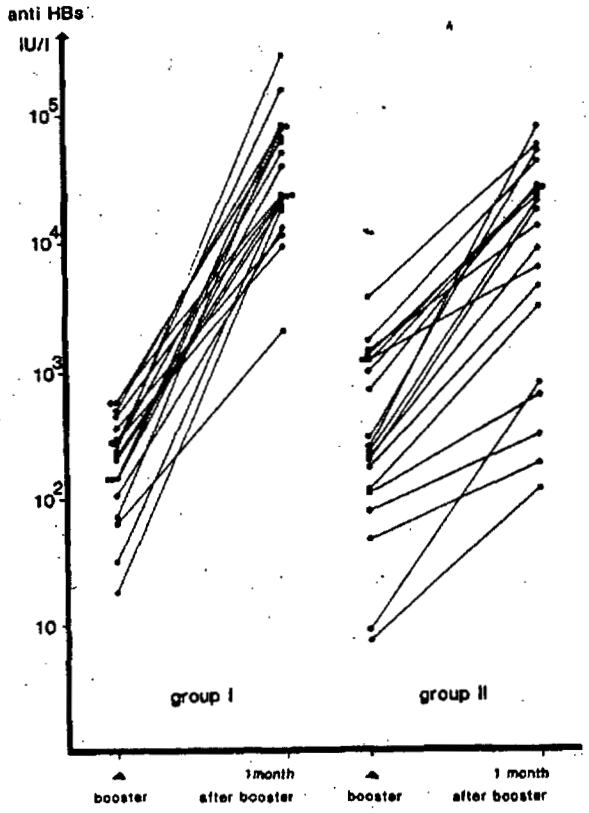

Fig. 2. Effect of the booster injection in individual vaccinees of group I and group II. Anti-HBs concentrations at the time of the booster injection (month 12 in group I, month 6 in group II) and one month later are shown.

et al, 1982]. An analysis of the anti-HBs concentrations during the course of immunization shows that after the first two injections with the Pasteur vaccine (at months 0 and 1) anti-HBs values were comparable to those obtained with the Merck vaccine [Goudeau et al, 1983; Brede et al, 1984; Zachoval et al, 1984], so it is likely that the higher anti-HBs concentrations seen after vaccination with the Pasteur vaccine are caused by a late booster injection given at month 12.

These findings have consequences for future vaccination strategies with the Merck hepatitis B vaccine, but also for vaccination with other similar hepatitis B vaccines consisting of purified HBsAg. The higher anti-HBs values obtained after a late booster should produce a longer persistence of anti-HBs and a longer protection against hepatitis B infection; a further booster injection, recommended when anti-HBs levels have decreased to or below a critical level of 10 IU/l [Jilg et al, 1985], may be postponed for some years. Thus, a better protection as well as a reduction of the costs of the vaccination may be achieved simply by a delay of six months in giving the booster injection. Our study shows that during the relatively long interval of 11 months between the second dose and the late booster, the anti-HBs concentration remains at a protective level; an initial increase in anti-HBs until month 6 is followed by only a slow decrease of about 35% during the next six months. Thus, at least in a young healthy population (<30 years of age), an immunization schedule using a booster at month 12 is acceptable. However, as our results are based on the investigation of a small group, they should be confirmed with larger numbers of vaccinees, especially with people from older age groups.

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