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Efficacy of Hepatitis B Virus (HBV) Vaccine in Long Term Prevention of HBV Infection

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SUMMARY **Efficacy of HBV vaccine in long term prevention of HBV infection was evaluated at 3 years after vaccination in 38 children and 61 adults. All vaccinees were negative for all HBV markers (HBsAg, anti-HBs and anti-HBc) before vaccination. Vaccines (Hevac B®) were given for 3 doses, one month apart, to 38 children aged 1 month - 14 years and 61 adults aged 15-45 years. After 3 years of vaccination, blood specimens were collected for the determination of HBsAg, anti-HBs and anti-HBc. The results revealed that no HBsAg antigenemia was found in all 99 vaccinees. Anti-HBs could not be detected in 4 children and 11 adults and this occurred only in the group of subjects who had initial anti-HBs less than 100 mIU/ml at 2 months after the last dose of vaccination. At three years after the first course of vaccination, 89.4 percent of children and 83.4 percent of adults still have anti-HBs above protective level (more than 10 mIU/ml) with geometric mean titers of 101 and 35 mIU/ml in children and in adult groups, respectively. The anti-HBc was detected in 2 out of 38 children and 10 out of 61 adults, but none of them became chronic hepatitis B carriers or developed clinical disease. It is recommended that everyone with anti-HBs values below 100 mIU/ml two months after the last dose of vaccine should be revaccinated with a booster dose within 6 months. Thsoe with anti-HBs levels higher than 100 mIU/ml, should be checked up at 3 years; if the anti-HBs is less than 10 mIU/ml, they should be revaccinated.**

Vaccination against hepatitis B virus (HBV) is currently the most important means of preventing HBV infection, and the clinical trials of HBV vaccine in one to two million individuals have proved it to be highly immunogenic, effective and safe.[1-3] However, like most other inactivated vaccines, after a course of active immunization with HBV vaccine, antibodies decline rather rapidly.[4,5] Earlier studies indicated that a booster dose of vaccination after five years was sufficient to maintain the antibody levels to hepatitis B surface antigen (anti-HBs) above 10 mIU/ml which is considered to be the minimal protective level,[6,7] 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.[4,8] Recently, a close correlation was demonstrated between the peak anti-HBs concentration after the basic immunization and the persistence of specific antibodies.[8-10] Vaccination strategies should therefore aim at the highest possible initial anti-HBs concentration, as this may ensure long-term persistence of anti-HBs and effective protection against HBV infection. In the study reported here, we examined the efficacy of HBV (Hevac B®) vaccine in long term protection of HBV infection in Thai children and adults after three basic immunizations at one month intervals, and the criteria for revaccination was proposed.

MATERIALS AND METHOD

Between January 1984 and October 1986, 938 normal Thai children and adults, aged 1-50 years, were screened for hepatitis B virus markers including hepatitis B surface antigen (HBsAg), antibody to surface antigen (anti-HBs), and antibody to core antigen (anti-HBc). Those who were negative for HBsAg, anti-HBs and anti-HBc were selected for active pre-exposure immunization

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with hepatitis B vaccine. The subjects comprised 176 healthy volunteer adults, 73 males and 103 females, aged 15-45 years and 162 randomised normal children, 83 males and 79 females, aged 1 month to 14 years. All subjects received three injections of 5 μg hepatitis B vaccine (Hevac B®) intramuscularly at one month intervals. Follow ups for side effects or complications were done after administration of each injection. The serological tests for quantitative anti-HBs were done two months after the last injection was given. The serum samples showing negative results for anti-HBs (non-responders) were further tested for HBsAg and anti-HBc. Among the responders (anti-HBs higher than 10 mIU/ml at 2 months after last dose of HBV vaccine), long term follow up for three years were available in 99 vaccinees, 38 children and 61 adults, Serum samples at 36 months after the last injection of HBV vaccine from these subjects were quantitatively measured for anti-HBs, anti-HBc and HBsAg. The anti-HBs level of these 99 vaccinees and the long term protective efficacy of HBV vaccination at 36 months were evaluated in relation to their initial antibody response at 2 months after last dose of vaccination.

Blood specimens were tested for HBsAg by a reverse passive haemagglutination method (RPHA antihebgencell, Green Cross, Osaka) and by an enzyme-linked immuno sorbent assay (Enzygnost HBsAg micro, Berhringwerke, Marburg), and for anti-HBs and anti-HBc by passive haemagglutination method (PHA hebgencell and core cell, Green Cross, Osaka) and by an enzyme-linked immunosorbent assay (Enzygnost anti-HBs and Enzygnost anti-HBc micro, Behringwerke, Marburg). Although ELISA method is more sensitive than RPHA or PHA method, it is more expensive. For economic reasons, we therefore screened the specimens first with the RPHA method for HBsAg and PHA method for anti-HBs and anti-HBc. Those specimens with negative results were further tested by ELISA method. The quantitative measurement of anti-HBs that developed after vaccination was done by ELISA method using WHO reference standard supplied in the test kit. The statistically significant differences were tested by either the chi-square test or the student's *t*-test where appropriate.

RESULTS

The results of active pre-exposure immunization in 176 healthy volunteer adults and 62 randomized children have been reported previously.[3] Seroconversion at 2 months after the third dose of vaccine was 96.30 percent in the children and 92.00 percent in the adults with mean anti-HBs titres of 800 mIU/ml and 353 mIU/ml, respectively. Among 99 responders which were followed up to 36 months, 4 out of 38 (10.6%) children and 11 out of 61 (16.6%) adults had lost their immunity (anti-HBs less than 10 mIU/ml). Whereas 89.4 percent of children and 83.4 percent of adults still had anti-HBs above protective level (more than 10 mIU/ml) at three years, the antibody levels were significantly decreased with geometric mean titers of 101 and 35 mIU/ml in children and in adults, respectively (Table 1). When the anti-HBs levels at 2 months after last dose of vaccination in 99 vaccinees were divided into 3 groups with 10-99, 100-999, and more than 1,000 mIU/ml and the anti-HBs levels at 36 months were compared with their initial antibody levels in each group, it was found that the anti-HBs disappeared at 3 years only in the group with had the anti-HBs level 10-99 mIU/ml two months after initial vaccination. All of subjects with the initial anti-HBs titer greater than 100 mIU/ml at 2 months still had anti-HBs values above 10 mIU/ml at 3 years and the greater the initial immune response at 2 months, the higher the anti-HBs levels remained at 36 months (Table

Table 1. Antibody response to hepatitis B vaccine (Hevac B ®) in 38 healthy children and 61 adults.

Subjects		At 2 months		At 36 months	
		Anti–HBs (mIU/ml)		Anti–HBs (mIU/ml)	
	No	Group	mean GMT	mean GMT	No. (%) < 10 mIU/ml
Children age 1/12–14 years	12	10–99	22	22	4 (33.3)
	13	100–999	350	95	0
	13	⩾ 1000	1,840	270	0
Total	38		246	101	4 (10.6)
Adults age 15–45 years	24	10–99	30	12	11 (45.8)
	32	100–999	252	47	0
	5	⩾ 1000	1,000	87	0
Total	61		122	35	11 (16.6)

1). Although the anti-HBs level declined with time in most cases, it was increased in 5 children; only 3 such cases were found in the adult group. At 36 months, no HBsAg-antigenemia was found in all 99 vaccinees, however the anti-HBc was detected in two children and ten adults, but neither clinical nor chemical hepatitis was observed.

DISCUSSION

Vaccination against hepatitis B virus is now an accepted preventive measure for people in endemic areas and those who are at high risk of hepatitis B,e.g., medical staff, close contacts of chronic carriers of HBsAg and homosexuals. However, the antibody levels to HBV vaccine decline with time and the risk of HBV infection increases as antibody is reduced below the protective level. There is still uncertainty about how long the persistence of anti-HBs will last after vaccination and about the need for and timing of revaccination. Our previous study showed that active immunization with HBV plasma derived vaccine (Hevac B®) in good schedule and optimal dose was highly effective in preventing the HBsAg carrier state in non-immune children and adults.[3] Seroconversion was observed in more than 90 percent of vaccinees with rather high titer of anti-HBs at 2 months after the last dose of vaccination. Three years after the third vaccine infection in 99 vaccinees, anti-HBs concentrations had fallen below 10 mIU/ml only in four children and eleven healthy adults who had initial anti-HBs levels between 10-99 mIU/ml but in none of those whose antibodies had originally been high than 100 mIU/ml. This findings is in accordance with the previous reports. Jilg *et al.* observed that among subjects with initial anti-HBs level less than 1,000 mIU/ml, 30.5 percent showed an anti-HBs level below 10 mIU/ml at 36 month while all vaccinees with initial anti-HBs more than 10,000 mIU/ml had anti-HBs value above 100 mIU/ml even after 4 years.[8] Similar, Laplanche *et al.* reported that 33.3 percent of subjects with initial anti-HBs titer less than 1,000 mIU/ml showed an anti-HBs level below 10 mIU/ml at 38 months, whereas 100 percent of subjects with an initial anti-HBs titer greater than 1,000 mIU/ml still had anti-HBs levels above 10 mIU/ml even after 5 years.[9] These findings indicate that the persistence of antibodies depended on the maximum anti-HBs concentration reached initially. The anti-HBs behaved typically in most individuals, reaching maximum levels in 1-2 months after the third vaccine injection and then fell rapidly leading to 90 percent reduction in the first 24 months.

Subsequently the decrease was slower; anti-HBs was reduced by about 50 percent from 2-4 years after the first vaccination.[8,10] In our study,the geometric mean titer of detected anti-HBs levels three years after the third vaccine injection was lower in adults (35 mIU/ml) than in children (101 mIU/ml, $p < 0.05$), but still higher than 10 mIU/ml which is considered to be the minimal protective level.[6] As anti-HBs levels declined below 10 mIU/ml in some of those who initially had low antibody level, the possibility of HBV infection increased. However, this was manifested by hepatitis B core antibody seroconversion alone in most cases. Anti-HBc were detected in two children and ten adults and the anti-HBs levels at 36 months were higher than the initial anti-HBs levels in 5 children and 3 adults, suggesting that these vaccinees had been boostered by the subclinical natural source of hepatitis B infection. More importantly, none of the responders in our study have become chronic hepatitis B carrier or developed clinical disease during these three years of follow up. No persistent HBsAg was detected in all vaccinees up to 3 years.

According to the results obtained from this study, we recommend that everyone with anti-HBs values below 100 mIU/ml two months after the last dose of Hevac B® vaccine should be revaccinated with a booster dose within 6 months. Those with anti-HBs levels higher than 100 mIU/ml, should be checked up at 3 year after the first vaccination; if the anti-HBs is 10 mIU/ml or less, they should be revaccinated.

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