Immunogenicity of low-dose and conventional-dose recombinant hepatitis B vaccines in healthy adolescents in India

S S Rana, R Singhal, R K Gupta, D Sharma, P Kar

ABSTRACT

Introduction: The recombinant hepatitis B vaccine, at a conventional dose of 20μg, is highly effective in a majority of the population. Recent studies have reported that a 10μg dose is as effective as the conventional dose, especially in young adolescents. This study compares the effect of two different doses of recombinant hepatitis B vaccine (Enivac HB) in healthy adolescents.

Methods: Ninety-two adolescents were randomised into two equal groups to receive either 10μg (group 1) or 20μg (group 2) of vaccine using the vaccination schedule of 0, one and six months. Blood samples were collected at 30, 60, 90, 180 and 210 days to detect anti-HBs antibodies. At each interval, geometric mean titres were calculated for seroconverted subjects.

Results: After the initial doses of the vaccine, greater proportion of subjects receiving the higher dose seroconverted. However, at six months, all subjects who received the low dose seroconverted, as did those who received the conventional dose. Furthermore, there were significant differences in the anti-HBs geometric mean titres for seroconverters at 180 days (218.27 versus 111.43) and 210 days (345.14 versus 133.35). The difference in the overall reactogenicity for the two dose levels was not remarkable, although the higher dose produced more local symptoms.

Conclusion: 10μg recombinant vaccine can be used in routine immunisation in healthy adolescents. If quick immunisation is needed, as in high-risk groups, the conventional dose should be administered, as it results in earlier seroconversion with higher anti-HBs geometric mean titres.

Keywords: hepatitis B, immunisation, low-dose hepatitis vaccine, recombinant vaccine, vaccination

Singapore Med J 2004 Vol 45(9):427-429

INTRODUCTION

Infection with the hepatitis B virus (HBV) is one of the biggest global health problems with an estimated 350 million chronic HBV carriers worldwide[1]. The development of an effective vaccine against HBV has contributed significantly in preventing infection. The recombinant vaccine, administered at the conventional dose of 20μg, is highly effective in a majority of the population[2]. It has been demonstrated that routine immunisation in infants will eventually produce broad population-based immunity to HBV infection, thus preventing HBV transmission in all age groups. However, to hasten the development of population-based immunity and to lower the incidence of hepatitis B infection, vaccination of all children and adolescents is recommended[3]. Moreover, age is a major determinant of vaccine response, with young children and adolescents having higher seroconversion rates[4].

Many authors have demonstrated that low-dose recombinant hepatitis B vaccine is as effective as the conventional dose, especially in adolescents[5,6]. To assess the immunogenicity of low-dose recombinant hepatitis B vaccine in adolescents in India, we evaluated the efficacy of a 10μg dose of recombinant hepatitis B vaccine. This dosage level was chosen to counter any loss of vaccine potency that might occur during lengthy transport or poor storage conditions and to increase the likelihood of producing a protective antibody level in all subjects, especially those having low immune responses[6]. If this low dose is found to be as effective as the conventional dose in healthy adolescents, the results would accelerate the pace of the immunisation programme.

METHODS

The subjects were healthy adolescents recruited from a secondary school in New Delhi, India. The hospital ethical committee approved the project. The rationale, risks, benefits and procedures were explained to the parents of the subjects and informed written consent was obtained prior to participation. The study population was selected based on two criteria. First,

Division of Gastroenterology
Department of Medicine
Maulana Azad Medical College
New Delhi, India

S S Rana, MD
Senior Resident

R K Gupta, MSc
Senior Research Fellow

P Kar, MD, DM
Professor

Department of Medicine
Lady Hardinge Medical College
New Delhi, India

R Singhal, MD
Senior Resident

Panacea Biotec, India

D Sharma, MD
Medical Advisor

Correspondence to:
Prof Premasis Kar
D 11/M 2755
Netaji Nagar
New Delhi 110023
India
Tel: (91) 11 2688 9271
Fax: (91) 11 2323 0132
Email: premashish_kar@rediffmail.com

Table I Seroconversion rates (%SR) and geometric mean anti-HBs titres of 92 subjects enrolled in the study.

Group	Blood sampling (days)	No. of subjects	SR (%)	GMT (mIU/mL)
Low dose	30	46	80.9	25.2
(10μg)	60	46	91.5	36.8
	90	46	97.9	54.4
	180	46	100	111.4
	210	46	100	133.4
Conventional	30	46	86.7	37.5
dose (20μg)	60	46	97.8	53.0
	90	46	100	77.1
	180	46	100	218.3
	210	46	100	345.1

GMT: geometric mean titre,

SR: seroconversion rate

the subject must be between 12 and 18 years of age. Second, they must test negative for HBsAg, anti-HBc and anti-HBs. Subjects with a history of significant or persistent haematological, hepatic, renal, cardiac or respiratory diseases, immunosuppressive therapy and simultaneous participation in other clinical trials were excluded from the study.

One week prior to the first vaccination (at month 0), a physical examination and interview were carried out. Ninety-two adolescents were randomised into two equal groups to receive vaccine containing either 10μg (group 1) or 20μg (group 2) of recombinant HBV vaccine (Enivac HB, Panacea Biotech, Okhla, Delhi, India). The vaccine was administered intramuscularly in the deltoid region at 0, one and six months in all subjects. Prior to the vaccination, 10ml of blood was drawn from each subject for serological analysis. Blood samples were also collected at 30, 60, 90, 180 and 210 days to detect anti-HBs antibodies. All blood samples were centrifuged, and the serum was separated and stored at -20ºC. Pre-immunisation samples were screened for HBsAg, anti-HBc, HBeAg, anti-HBe and anti-HBs using ELISA kits. Seroprotective subjects had anti-HBs titres ≥10 IU/L. At each interval, geometric mean titres (GMTs) were calculated for seroconverted subjects.

All subjects were monitored for 30 minutes after injection. The parents recorded any local and systemic reactions for three days after each injection. They were also asked to record any adverse events and illness that require medical attention between day three after vaccination and the next visit. Serious adverse events were to be reported at up to 30 days after the last vaccination visit.

The immunogenicity data of available blood samples were analysed and presented on a per-protocol basis. Seroprotection and adverse reaction were compared between the two groups using chi-square test or Fischer's exact test wherever appropriate. Quantitative analysis was performed using two-sided Student's t-test after logarithmic transformation of the antibody titres.

RESULTS

All 92 subjects included in the study completed the trial and none were lost to follow-up. Both the groups were comparable in age and gender. The mean age was 14.06 ± 1.09 years and 14.08 ± 1.04 years in group 1 and 2 respectively. Table I shows the seroconversion rates in both groups at 30, 60, 90, 180 and 210 days. Six months after the first dose, all subjects seroconverted in both groups. However, the GMTs were significantly higher in the group that received the conventional dose (Table I). This difference was also significant at the end of the trial. The GMTs in the low dose group were 111.43 and 133.35 at the end of six and seven months, respectively; in the conventional-dose group, these were 218.27 and 345.14, respectively.

Local and general reactions were generally mild and lasted for <48 hours. In both groups, local symptoms were more common than general symptoms. There was no significant difference in adverse reactions in both groups. The incidence of local and general symptoms in both groups decreased from the first to the third dose. Both doses were well-tolerated.

DISCUSSION

The availability of a safe, immunogenic and effective hepatitis B vaccine has helped to prevent hepatitis B infection[7]. The protective efficacy of hepatitis B vaccination is directly related to the development of anti-HBs[8]. Subjects who develop anti-HBs titres exceeding 10mIU/mL after a primary vaccination series are completely protected against clinical illness and chronic infection. The recommended series of three intramuscular doses of hepatitis B vaccine induces a protective response in more than 90% of healthy adults that are less than 40 years old[9].

All subjects in the low-dose group seroconverted at day 180, as did those who received the conventional dose. This implies that 10μg of vaccine provides adequate protection in healthy adolescents. Other studies have demonstrated that 10μg of the vaccine achieves similar rates of seroprotection as the conventional dose[5,6]. However, most of these studies noted that the seroprotection rates after two doses of vaccine are significantly higher among adolescents receiving the conventional dose rather than the low

dose[6]. This is an important finding in youths who may not be able to complete the vaccination series.

In our study, there was no significant difference in the seroprotection rates between the two groups after two doses of vaccine. Our results for the conventional dose compare with earlier published results from India, which have shown that the seroconversion rates after two conventional doses of recombinant vaccine in healthy adults is between 95% and 100%[10]. Although there is no current data on the protective efficacy after two doses of low-dose hepatitis B vaccine, it is reassuring to note that a high percentage of vaccines would probably be protected based on the antibody response.

It is also known that immunological priming would result in higher protection rates, as children and adults who developed antibody concentration ≥10mIU/mL after vaccination have shown immunological memory even after antibody concentrations have fallen below 10mIU/mL[11]. Thus, even if adolescents do not complete the vaccination schedule with low dose, the first or second dose will provide immunological priming. Thereafter, whenever the adolescent encounters the healthcare system, additional doses can be given. The intervals between the first and third dose, at up to 12 months are associated with higher geometric mean antibody titres; the longer the interval, the higher the final antibody concentration[12]. Thus, low-dose recombinant hepatitis B vaccine produces acceptable seroprotection rates in adolescents.

The GMTs achieved with a low dose were significantly lower than those achieved with a conventional dose. Similar results have been reported by centres around the world[13]. While many studies have shown that the 20μg dose of recombinant hepatitis B vaccine results in higher seroconversion rates after one or two doses than the 10μg dose, and that the mean antibody titres achieved are also less with the low dose, it is suggested that conventional dose regimen should be used if there is a high risk of hepatitis B. As vaccine cost is an important factor, it makes sense to vaccinate with the lowest effective dose. As has been shown, the 10μg dose is as effective as the conventional dose, this will double the manufacturing output and lower vaccine cost, thus boosting immunisation programmes.

In conclusion, the 10μg dose of recombinant hepatitis B vaccine in healthy adolescents is safe, well tolerated and immunogenic. However, when there is a high risk of hepatitis B, the conventional dose should be used in immunisation.

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