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Full Length Research Paper

Assessment of immune response and safety of two recombinant hepatitis B vaccines in healthy infants in India

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Hepatitis B infection and its sequel continue to be a worldwide health problem, especially in the developing countries. The pool of chronic carriers of hepatitis B virus is built up in childhood and is then maintained in older children and adults. Therefore, it is important to give protection during infancy. Effective vaccines to prevent hepatitis B infection are available. This study was undertaken to evaluate the immune response and reactogenicity of two recombinant hepatitis B vaccines available in Indian market, in normal healthy infants. Infants of 6-8 weeks of age were screened for eligibility criteria. All the eligible subjects had negative baseline serum HBsAg and anti-HBs. The subjects received three doses of 10 µg of Gene Vac-B or Engerix-B at 6, 10 and 14 weeks of age. GeneVac-B is an indigenously manufactured vaccine, while Engerix-B is an imported vaccine. The vaccinees were assessed for immune response and safety parameters. The anti-HBs antibody titer was obtained 1 month after 3rd dose of vaccine and was considered seroconverted if more than 1 mIU/ml, and seroprotective if more than 10 mIU/ml. Total of 126 subjects were considered for analysis. One month after 3rd dose, seroconversion was 100% for both the vaccines and seroprotection was 94.36% for Gene Vac-B, and 92.72% for Engerix B. The GMT of anti- HBs antibodies were 149.47 mIU/ml for Gene Vac- B and 153.28 mIU/ml for Engerix B. Four cases of incessant cry were observed during the study period. The indigenous vaccine, Gene Vac-B and the imported vaccine, Engerix-B showed high immunogenicity and safety profile in Indian infant population. Both vaccines were comparable.

Key words: Hepatitis-B vaccine, gene vac-B, infants, immunogenicity, reactogenicity.

INTRODUCTION

Hepatitis B virus (HBV) infection and its sequel continue to be a worldwide health problem, especially in the developing countries. HBV is acquired primarily by parenteral routes (WHO, 2004). The younger the age of the infection, the higher the chances of becoming a chronic carrier. Infection acquired during infancy is rarely cleared up, and more than 90% of infected infants develop chronic infection. In this case, the signs and symptoms may not be evident for many years and may end up with chronic liver diseases later in life (WHO, 2004; McMahon et al., 1985).

In India, overall prevalence of hepatitis-B is 2.4% (Batham et al., 2007). Community studies indicate that about 3 to 5% of children below 5 years of age are carriers of HBsAg with horizontal transmissions playing an important role (Lodha et al., 2001). It is also revealed that the pool of chronic carriers of hepatitis B virus is built up in childhood and is then maintained in older children and adults (Singh et al., 2000). Despite the introduction of hepatitis B vaccines in the immunization schedule for many years in India, drastic reduction in the prevalence

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rate has not yet been achieved because it may take decades to achieve the same as the Hepatitis B virus has penetrated deeply the population both horizontally and vertically.

All these issues highlight the need of completing hepatitis B immunization during infancy. The Indian Academy of Pediatric (IAP) has recommended HBV vaccination in Indian infant population in line with the recommendation of the World Health organization (WHO) (IAP guidebook on Immunization, 2007).

Serum Institute of India Ltd., Pune, India has developed an indigenous recombinant vaccine; Gene Vac-B which was licensed in 2001. The vaccine provides adequate protection against HBV in adults (Vijayakumar et al., 2004; Kulkarni et al., 2006), adolescents (Vijayakumar et al., 2004; Kakrani et al., 2003), and infants (Shivananda et al., 2006; Sapru et al., 2007). However, more information on the uniformity of the vaccine induced seroconversion efficiency of the vaccine is needed for every state of India. Therefore, this study was undertaken to evaluate further the immune response and reactogenicity of Gene Vac-B in comparison with Engerix-B (GlaxoSmithKline Beecham) in normal healthy infants from the city of Chennai in the state of Tamilnadu, when given at 6, 10 and 14 weeks of age.

MATERIALS AND METHODS

Study design

This was an open label, prospective study in healthy infants of 6 to 8 weeks of age. The study was conducted at Sahishnatha Vijaya Institute of Child Health, Vijaya Health Centre, Chennai, from December 2004 to June 2006. Parents of the infants were fully informed about the study, and written informed consent was obtained before subject participation. Total of 204 subjects were screened for eligibility criteria. The study protocol was approved by the institutional ethics committees of Dr. ALM Post Graduate Institute of Basic Medical Science, University of Madras, Taramani, Chennai, India, and Sahishnatha Vijaya Institute of Child Health, Vijaya Health Centre, Chennai.

Study vaccines

The recombinant vaccine, Gene Vac-B was derived from *Hansenula polymorpha* (yeast) with aluminum hydroxide (≤1.25 mg) as adsorbent and thiomersal (0.01) as preservative. The dose of vaccine was 0.5 ml (10 µg). The vaccine (Batch No: S-50313, MFG date: Dec-2004, expiry date: April 2006) was provided by the Serum Institute of India limited, Pune.

Engerix- B vaccine (Batch No: AhBv B 035AA, MFG date: February-2004, expiry date: January 2007) was used to compare the efficacy of Gene Vac-B Vaccine. It is derived from the yeast *Saccharomyces cerevisiae* with same adsorbent and preservative.

Vaccines were administered intramuscularly in the antero-lateral region of thigh by paramedical personnel.

Study population

The healthy infants of 6 to 8 weeks of age, of both sex, and whose parents gave the written informed consent were included in the study. The exclusion criteria were acute febrile illness, any other infection, evidence of skin disease, conditions associated with immunosuppression, infants receiving immunosuppressive therapy, previous hepatitis B vaccination, hypersensitivity to any component of vaccine, presence of HBsAg or Anti-HBs antibody and participation in any other clinical trial one month before and during the course of study.

Methodology

After signing the informed consent, medical history was taken from parents and infants were subjected to clinical examination. Blood samples were collected by paramedical personnel before the vaccination for HBsAg, and anti-HBs antibodies. The subjects were vaccinated with 0.5 ml of either Gene Vac- B or Engerix-B by simple randomization at 6, 10 and 14 weeks of age along with DTP vaccine.

The subjects were followed till 1 month after 3rd dose. Medical history and physical examination were conducted in all four visits. The parents were informed to carefully monitor the child for any adverse events and communicate to the pediatricians immediately. The blood samples were again collected one month after 3rd dose for serum anti-HBs antibodies.

Serology

All serum samples from the vaccinees were assayed for the quantitative levels of anti HBsAg antibodies using Diasorin anti-HBs 3.0 kits. The anti-HBs standards, supplied by M/s Sanofi Pasteur, France were used to develop the calibrated linear graph by the software installed in the ELISA reader- Biotech model EL_X 800. A titre of ≥ 1 IU/ml was interpreted as seroconversion and a titer ≥ 10 IU/ml was considered as seroprotection.

Geometric mean titres (GMT) of anti HBs were calculated by taking anti-log of mean of log transformed anti-HBs antibody concentrations. Proportion of seroconversion and seroprotection in percentages were compared between groups using Fisher's exact test. GMT of anti HBs antibodies were compared between groups using Mann-Whitney test. Seroconversion and seroprotection rates between males and females of both groups were also tested by Fisher's exact test. GMTs between males and females were tested by Mann-Whitney test in both the groups. P value (≤ 0.05) was considered statistically significant.

RESULTS

A total of 204 normal healthy subjects were screened for eligibility criteria. 24 children (HBsAg positive -7, anti-HBs antibody -17) were found to be screening failure. 54 subjects failed to report on follow up visit. Therefore, a total of 126 subjects were considered for final analysis, wherein, 71 subjects had received Gene Vac-B vaccine and 55 subjects received Engerix-B vaccine. 52% were male in Gene Vac-B group and 61% in Engerix-B group.

The percentages of post-vaccination seroconversion were 100% in both vaccine groups. Similarly, the percentages of post-vaccination seroprotection were 94.36 and 92.72% in Gene Vac-B and Engerix-B group respectively (Table 1). The difference was not statistically significant (P > 0.05). GMT of anti HBs antibody in Gene Vac-B

Table 1. Immune response of the Gene Vac-B and the Engerix-B vaccine recipients 1 month after 3rd dose.

Parameter	Group I: Gene Vac-B (n = 71)	Group II : Engerix-B (n=55)
Seroconversion (N & %)	71 (100%)*	55 (100%)
Seroprotection (N & %)	67 (94.36%)*	51 (92.72%)
GMT (mIU/ml)	149.47*	153.28
GSD (mIU/ml)**	3.6940	3.3189
95% Confidence Interval	109.69- 203.65	110.84 -211.98

*: not significant (p ≥ 0.05); **: GSD, antilog of standard deviation of log-transformed titres.

Table 2. Gender wise analysis of immunogenicity of the two vaccines tested.

Parameter	Group I: Gene Vac-B		Group II: Engerix-B	
	Male (n = 37)	Female (n = 34)	Male (n = 34)	Female (n = 21)
Seroconversion	100 %	100 %	100 %	100 %
Seroprotection	97.29 %	91.17 %	94.17 %	90.47 %
GMT (mIU/ml)	122.80	185.13	161.17	141.31
GSD (mIU/ml)*	4.12	3.17	2.69	4.48
95% Confidence Interval	76.52-197.01	123.65-277.14	114.02-178.8	71.38- 279.38

*GSD, antilog of standard deviation of log-transformed titres.

group was 149.47 mIU/ml and that of Engerix-B group was 153.28 mIU/ml and was comparable in both vaccine groups (Table 1).

Gender wise analysis of serological results is given in Table 2. The seroconversion and seroprotection were similar in both genders in the vaccine groups. Similarly, there was no difference in the GMTs induced by both the vaccines on the basis of gender.

Table 3 shows distribution of subjects in both the groups according to antibody levels. Titres ranging from 5 to 1400 mIU/ml were seen in both groups, and the number of children showing different titration levels are almost the same in both groups. Incessant cry was the only adverse event reported during the study, which was observed in 2 subjects from each group after receiving 1st dose of the study vaccines. No serious adverse event was reported during the study period.

DISCUSSION

WHO recommends three-dose schedules of hepatitis-B vaccine during infancy in all the countries (WHO, 2004). This is especially relevant in India where the disease is highly endemic. The three doses regime at 6, 10, and 14 week is commonly practiced in India since it coincides with DTP and Oral polio vaccines. Naturally this schedule increases the compliance.

When administered in the complete series of 3 doses, 10 ∝g dose of hepatitis B vaccine usually gives protection to >95% of infants. Engerix-B induced a seroconversion of 98.5% when administered at 2, 4 and 6 months of age (Goldfarb et al., 1996). When administered to infants of 0, 1, and 6 months of age, Engerix-B showed 96% seroprotection (Goldfarb et al., 1994). Recombivax of Merck protected 99% of infants when administered at 2, 4, and 6 months of age (Greenberg et al., 1996). Another Indian vaccine, Shanvac-B, is also equally protective when administered in infants of 6, 10, 14 weeks of age (Velu et al., 2007).

Similarly, Gene Vac-B has shown high immunogenicity in earlier studies conducted in infant population. Shivananda et al. (2006) reported 96% seroprotection with GeneVac-B. Sapru et al. (2007) also found comparable results, wherein the first dose of Gene Vac-B was given at birth and second and third dose at 6, and 14 weeks. In another study involving high risk newborn infants born to hepatitis B surface antigen (HBsAg) positive mothers, Gene Vac-B was compared with Engerix-B and Shanvac-B. All infants were seroprotected for 1 year; irrespective of the vaccine they received (Velu et al., 2007).

The results of this study are in line with published literature on GeneVac-B and other recombinant hepatitis-B vaccines. Again, Gene Vac-B vaccine was found to be highly immunogenic. The seroconversion, seroprotection and GMT of anti HBs antibodies were comparable to those with Engerix-B.

When compared with different immunization schedules (0, 1 and 6 months[13] and 2, 4 and 6 months) (Goldfarb et al., 1994) evaluated in other clinical studies in infant population, vaccination schedule of 6, 10, 14 wks provides comparable immune response with added advantage of compliance of the subjects. One of the risk

Table3. Anti-HBs antibody titre in infants one month after 3rd dose.

Antibody titre (mIU/ml)	Group I: Gene Vac-B (n=71)	Group II: Engerix-B (n=55)
0-10	4 (5.6 %)	4 (7.3 %)
11-100	32 (45.1 %)	20 (36.4 %)
101-500	24 (33.8 %)	25 (45.5 %)
501-1000	10 (14.1 %)	4 (7.3 %)
>1000	1 (1.4 %)	2 (3.6 %)
Total	71 (100 %)	55 (100%)

factors associated with non-response to hepatitis B vaccine is supposed to be male gender (Kubba et al., 2003). However, this was not evident in our study. Seroconversion, seroprotection and GMT were similar in male and female infants with both the vaccines.

The distribution of subjects in both the groups according to antibody levels was also assessed. The distribution in various ranges seemed to be comparable in both the groups, with a majority falling above 100 mIU/ml titres.

Hepatitis B vaccines are considered one of the safest vaccines and serious adverse events are exceedingly rare (Plotkin and Orenstein, 1999). We found no difference in reactogenicity profile between the two vaccines. Incessant cry was reported in both vaccine groups. Both the study vaccines were very safe.

To conclude, the new Indian vaccine; Gene Vac-B is as immunogenic and safe as Engerix-B in infants. Moreover, there is an added advantage of cost effectiveness (IDR triple I, 2007). It is note worthy that China has brought down the HBV prevalence rate to 2.1% among all children and in 1.0% among children born after 1999 (Xiaofent et al., 2009).

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