

Tolerability of a Recombinant DNA Hepatitis B Vaccine -Results of Post-Marketing Surveillance

Sanjay Singh and Deepika. R. Sharma
(Received for publication : 12 January, 1999)

Hepatitis B virus (HBV) is the most important cause of hepatitis both in children and adults. Hepatitis B virus is distributed all over the world with a much marked infection level (5 - 20%) in Asia specially South East Asia, Person to person HBV transmission occurs through contact of slightly damaged skin or mucosa, infected body fluids like blood, semen and saliva. Direct transmission of the disease occurs from HBV carrier mother to their newborn children. Prevention of Hepatitis B by active immunization was achieved about 10 years ago with the advent of plasma-derived vaccines initially, and subsequently by recombinant DNA hepatitis B vaccines. A full immunization course in immunocompetent vaccines can probably elicit protection for 10 years or more¹. The World Health Organization (WHO) recommended in 1992 that all countries should introduce universal Hepatitis B vaccination in their immunization schedules by December 1997 and over 80 countries, many of them in Western Europe, have complied with this recommendation. A universal adolescent Hepatitis B vaccination program would result in the most immediate health benefits and speedy eradication of hepatitis B since man is the only natural reservoir of HBV.

Recombinant technology of Enivac HB (hepatitis B vaccine) involves the insertion of the segments of the HBV genome, which encode HBsAg, into a plasmid vector expressed in common yeast *Pastia pastoris* therefore, allowing the expression of HBsAg. The vaccine is manufactured under the principles governed by WHO Good Manufacturing Practices (GMP, WHO) and the product is marketed by different brand names in different countries. The product has demonstrated adequate seroconversion in all age groups in studies conducted in India and other countries. On the strength of clinical trial evaluation profile, millions of doses have been released in several countries since 1990 including India (since 1997). In India rccDNA Hepatitis B vaccine Enivac HB has been approved by the regulatory authority of the Ministry of Health and Family Welfare. Government of India for use as prophylaxis against Hepatitis B infections, The purpose of conducting post marketing surveillance study under field conditions was to assess the reactogenicity and safety of Enivac HB in unselected adults and children when administered in routine practice. Enivac HB was administered by deep intramuscular injection in the deltoid region of the arm with 2 doses at 1 - month interval followed by a third dose 6 months after the first dose (0-1-6 months).

[\(TOP^\)](#)

The vaccine was administered in the following dosages.

Children below 10 years of age :

- 10 micrograms of the antigenic protein in 0.5 ml of suspension per dose.

Adults and 10 years or older children :

- 20 micrograms of the antigenic proteins in 1 ml of suspension per dose.

Subjects having any evidence of liver disorder, severely immunocompromised individuals on immunosuppressant therapy, subjects with history of narcotic abuse and severe infection were excluded from the study. This was a prospective post marketing surveillance study conducted under routine practice in occupational health care setting with healthy adults and children without age limits. Staff and their relatives from government and public sector houses were comprehensively vaccinated and these included 459 subjects from Hero Honda Ltd, (Gurgaon). 288 subjects from Panacea Biotec (New Delhi), 375 subjects from National Thermal Power Corporation (New Delhi) and 3-300 subjects from National Thermal Power Corporation (NOIDA). When the first dose was administered at month 0, appointments were made for the second and third vaccination with the distribution of patient immunization cards. The month one time point for the second dose ranged from 30 to 38 days after the first dose and the time interval for the 6 month dose extended to a maximum of 20-30 days. This flexibility accounted for maximum number of vaccines to complete their full immunization course. All subjects were evaluated for 3 days after every dose of vaccine for the appearance of any side effects like fever, tenderness and pain at the site of injection, erythema, induration, headache/vomiting, swelling, rash, bodyache, fatigue and others

Out of a total of 5558 cards distributed, 5456 subjects were registered for completing the full vaccination compliance by their respective institutions, giving a compliance rate of 98.1%. Of these 3885 were males and 1571 females. Each subject was questioned verbally and reported in writing regarding the occurrence and severity of any local or general symptoms. During the approximate 7 month period of observation of each vaccinated person, any serious adverse event was to be reported within 24 hours by phone or fax to Panacea Biotec, Medical Department, New Delhi.

The incidence of side effects observed after administering the vaccine included 30 subjects (0.55%)

who developed pain at the site of injection, 20 subjects (0.37%) who developed fever and 12 subjects (0.22%) who experienced local reaction at the site of injection. These side effects appeared after 1st, 2nd or 3rd dose and did not last for more than 1 or 2 days Overall limit of reactogenicity was 1.14%.
A report of all these observations was submitted to the Directorate General of Health Services.

Authorities from the government department of the parent company had certified a document on adverse reactions occurrence after vaccination which states that between 1992 and March 1994 a total of 24,66,522 doses of Hepatitis B vaccine were distributed. Besides the slight and transient side effects found in the controlled clinical trials, only 2 reactions, in the form of a fine rash within the first three days after administration of the second dose, have been reported which is 0.08 per 1,00,000 vaccination doses administered (Ministry of Health, Cuba 1994).

In neonates the adverse reactions consisted of mild short lasting symptoms of fever, erythema and induration⁴. Major adverse effects to recombinant Hepatitis B vaccine are less frequent but nevertheless several reports of critical reactions have been published^{5,6}. These include skin lesions, rheumatic reactions, pulmonary and cutaneous vasculitis, systemic lupus erythematosus, ophthalmologic reactions, neurologic reactions like demyelinating disease of the central nervous system, chronic fatigue syndrome and hearing loss. These adverse effects are described as individual case reports from a large populations and their occurrence is absolutely minimum. The actual cause of such reactions has not been proven and it is believed that all these reactions are immune mediated in nature.

In our study, the post-vaccination surveillance conducted in 5456 adults and children has proved the vaccine to be safer and well tolerated in Indian subjects.

[\(TOP^\)](#)

REFERENCES

1. Wainwright, R.B., et al. Duration of immunogenicity and efficacy of hepatitis B vaccine in a Yupik Eskimo population. *JAMA* 1989. 26/(16); 2362-6.
2. Eduardo Penton., Varena Muzio. and Martha Gonzalez-Griego. The hepatitis B virus (HBV) infection and its prevention by a recombinant-DNA surface antigen (rec-HBsAg) Vaccine. *Biotechnologia aplicada* 1994. 11(1); 1-11.
3. Galban Garcia, E. et al. Field trial of the Cuban recombinant vaccine against hepatitis B (Heberbiovac HB) Study in newborn infants born to AgsHB +mothers. *Revista Cubana de Medicina Tropical* 1992, 44(2); 149-57.
4. Diaz Gonzalez. M. et al. Adverse reactions and immune response to Heberbiovac-HB vaccine administered to infants simultaneously with DPT and VA-MENGOC-BC]-*Revista Cubana de Medicina Tropical* 1997. 49(3); 196-203.
5. Grotto, I. et al (1998). Major adverse reactions to yeast derived hepatitis B vaccines - a review. *Vaccine* 1998. 16(4); 329-334.
6. Bonfils, P., et al (1996). Fluctuant perception hearing loss after hepatitis B Vaccine. *Annales D Oto-Laryngologie et de chirurgie Cervico-Faciale* 1996 113(6); 359-61.

Department of Clinical and Medical Research, Panacea Biotech Ltd. B-1 Ext/ A
- 27, Mohan Co-op. Ind. Estate, Mathura Road, New Delhi - 110 044.