Original article

Immunogenicity of hepatitis B vaccine (HEVAC B) in children with advanced renal failure

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Abstract. The immune response after hepatitis B (HB) vaccine HEVAC B was studied in 33 children (mean age 10 ± 4 years) with advanced renal failure. Responders and protected patients were defined by antibody titres to HB surface antigen (anti-HBs) of greater than 10 and 50 mIU/ml, respectively. All received the initial recommended three injections at monthly intervals, and 23 received a booster injection (I3) 11 ± 1 months after the third injection (I3). Loss of protection after I3 led to additional injections in 8 patients (25%). Vaccine was well tolerated and no HB infection occurred during the follow-up period (19 ± 10 months). The percentage of responders was 91% 2 ± 1 months after I3, and 100% 1 month, 13 ± 1 months and 26 ± 2 months after I3. The percentages of protected patients at these dates were 91%, 95%, 100% and 100%. Anti-HBs titres 1–3 months after I3 were useful for indicating those patients likely to have a rapid decline in anti-HBs titres, thus requiring serial anti-HBs determinations and additional injections to prevent a loss of protection. We conclude that, at the expense of a reinforced vaccination schedule in 25% of patients, HEVAC B vaccine can safely achieve a sustained protection in more than 90% of uraemic children.

Key words: Hepatitis B vaccine – Chronic renal failure – Haemodialysis

Introduction

Vaccination against hepatitis B (HB) is justified in uraemic patients in order to reduce the number of HB surface antigen (HBsAg) chronic carriers, who are at risk from life-threatening complications after renal transplantation [1]. Immunogenicity of HB vaccination in adults has proven to be satisfactory in healthy patients [2, 3] but poor in patients on haemodialysis (HD) [4–6]. Satisfactory immunogenicity has been observed in healthy children [7, 8], as well as in a few series of uraemic patients [9, 10]. In the present series, 33 uraemic children, 24 on HD, were vaccinated with the HB vaccine HEVAC B. This retrospective study was performed to assess: (1) the percentage of seroconversion and seroprotection in this population, and (2) the usefulness of sequential antibody determinations for the identification of patients requiring additional injections to maintain a protective level.

Patients and methods

Thirty-three children (20 males) were vaccinated against HB (HEVAC B, plasma-derived vaccine, Institut Pasteur Production, Marnes-la-Coquette, France) between 1980 and 1986. At the time of the first injection, mean age was 10 ± 4 years, and mean weight 30 ± 11 kg. Twenty-four children were on chronic HD; creatinine clearance was 16 ± 7 ml/min per 1.73 m² in the other 9. Five of these started HD during the study. Patients had no serological evidence of previous HB virus infection and transaminase levels were normal at the time of the first injection. One child became positive for human immunodeficiency virus (HIV) during the 3rd month of vaccination, after a contaminated blood transfusion. During the study period, 2 HBsAg chronic carriers were occasionally dialysed in the unit.

Transaminases, HBsAg, antibody against HBsAg (anti-HBs) and antibody against core antigen (anti-HBc) were checked every 3 months in children on HD and every 3–6 months in non-dialysed patients. Radio-immunoassay or enzyme immunoassay (Abbott Laboratories, Chicago, Ill., USA) were used to detect HBsAg (AUSRITA, AUZYME), anti-HBs (AUSAB RIA, AUSAB EIA) and anti-HBc (CORAB, CORZYME). Patients were considered as responders when the anti-HBs level was greater than 10 mIU/ml. Anti-HBs levels greater than 50 mIU/ml were considered as protective [2].

Each injection of vaccine consisted of 1 ml of HEVAC B (5 µg HBsAg). Thirty-three children received the initial recommended three injections. As the follow-up period was less than 1 year in 10 children, only 23 children received a booster injection (I3) 11 ± 1 months after the 3rd injection (I3). Because anti-HBs titres remained less than 50 mIU/ml, an additional injection was given 5 ± 2 months after I3 in 8 children (25%), and again 5 months after I3 in 1. In addition, because of undetectable anti-HBs, 4 of these children received a double dose (2 ml). Thirteen patients on HD received HB immune globulin concomitantly.
with the first three injections because of the presence of an HBsAg chronic carrier in the unit.

Student’s t-test and the chi-square test were used for statistical analysis. Anti-HBs values were expressed as geometric mean titres (GMT)±1 standard deviation.

## Results

Vaccine was well tolerated without local side-effects. No HB virus infection occurred among the vaccinees during the follow-up period (mean duration 19±10 months). All children remained negative for HBsAg. Anti-HBc titre were transiently positive in 4 children 1–2 months after HB globulin administration. A transient (<2 months) and mild elevation of transaminases (43–340 mIU/ml, normal <40) was noticed in 3 children on HD without serological evidence of hepatitis A, cytomegalovirus, or Epstein-Barr virus infection.

Anti-HBs titres after the first three injections and the booster are summarized in Table 1. Overall, 30 of 33 (91%) and 22 of 24 (91%) patients seroconverted 2±1 months and 1±1 months after I3, respectively. These patients remained responders 1 month, 13±1 months and 26±2 months after I8. Three patients remained non-responders after I6. One was lost to follow-up. The second had a slight rise in anti-HBs titre (240 mIU/ml) despite additional injections but was lost to follow-up thereafter. The third child became positive for HIV just before I3. He had a small rise in anti-HBs titre (33 mIU/ml) after I8 with subsequent low titres despite a 8 ml cumulative dose.

Overall, 30 of 33 (91%) and 16 of 24 (67%) patients developed anti-HBs titres of more than 50 mIU/ml, at 2±1 months and 11±1 months after I3, respectively. The proportion was 20 of 21 (95%) 1 month after I8. All patients had anti-HBs titres greater than 50 mIU/ml, 13±1 and 26±2 months after I8.

Sequential anti-HBs determination between I3 and I8 was performed in 25 patients. Anti-HBs titres less than 50 mIU/ml before I8 were observed in 12 children whose anti-HBs titres ranged between 0 and 410 mIU/ml 2±1 months after I3. On the other hand, anti-HBs titres 2±1 months after I3 were less than 410 mIU/ml in 16 patients and greater than 410 mIU/ml in 9. Anti-HBs titres less than 50 mIU/ml between I3 and I8 occurred in 75% (12/16) in the former and 0% in the latter (P <0.01). In addition, anti-HBs GMT 1 month after I8 were significantly lower in patients with anti-HBs less than 410 mIU/ml 2±1 months after I3 (1300 vs 17818 mIU/ml, P <0.01).

No statistically significant differences were found between the 8 patients who required additional injections, and the 25 children who did not, for age (9.6 vs 10.11 years), weight (24 vs 26 kg) and the proportion of patients on dialysis (81% vs 83%) or injected with immunoglobulin (29% vs 36%).

In those patients who received immunoglobulins, anti-HBs titres 3±2 months after I8 did reflect active immunogenicity rather than passive injected antibodies, as they were significantly higher than anti-HBs titres 1 month after the first vaccine and immunoglobulin injections (2980 vs 134 mIU/ml, P <0.01).

## Discussion

While numerous publications have reported the results of HB vaccine in healthy adults [2, 3] or adults on HD [4–6, 11, 12], only three papers have been devoted to this subject in children with chronic renal failure (CRF) [9, 10, 13]. In the present series of 33 patients, we confirmed the safety and immunogenicity of HEVAC B vaccine in children with CRF. Seroconversion was achieved in 91% of patients after three injections and in 100% of patients after a booster. These results are similar to those of Nivet et al. [10] who obtained a 100% seroconversion rate after the third and the booster injections of HEVAC B in 10 uraemic children. Similarly, Callis et al. [9] reported a seroconversion rate of 81% after two injections of HEPTAVAX B (Merck, Sharp, and Dohme, West Point, Pennsylvania, USA) and 88% after booster in 18 uraemic children. Bergamini et al. [13] reported seroconversion in only three of six uraemic children after three injections of HEPTAVAX B. Our results are in the same range as those reported in healthy adults [2–4, 14], children [15] and infants [7, 8] after HEVAC B [2, 8, 14] or HEPTAVAX B [4, 7, 15]. Lower seroconversion rates, from 63% to 82%, were observed in adults on HD after either vaccine [4–6, 11, 12]. These results confirm that young age probably contributes to a better immune response in patients with

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<tr>
<th>Table 1. Antibody (anti-HBs) response after administration of hepatitis B vaccine HEVAC B</th>
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<tr>
<td>Months after 3rd injection</td>
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<td>2±1</td>
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<tr>
<td>No. of patients</td>
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<tr>
<td>Anti-HBs GMT (mIU/ml)</td>
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<td>No of patients with seroconversion</td>
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<td>No. of patients with anti-HBs &gt;50 mIU/ml</td>
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Anti-HBs GMT, Geometric mean titre of antibody to hepatitis B surface antigen

a Values in bracket's denote geometric mean ± 1 SD