

IMPROVEMENT OF IMMUNE RESPONSE IN DIALYSIS PATIENTS TO HEVAC B VACCINE AFTER MULTIPLE INJECTIONS OF VACCINE

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Summary

From December 1981 to April 1984, 56 dialysed patients were enrolled in a vaccination programme in which HBIg and Hevac B were repeated monthly until an active anti HBs response could be demonstrated (anti HBs ≥ 33 mU more than 60 days after the last 4ml of HBIg). Among 39 patients (25 men, 14 women, mean age 59) the proportion of vaccine responders increased from 44 per cent, to 67 per cent, to 82 per cent and 90 per cent when the number of injections increased from four to six, 10 and 14. Older age, sex (male) and duration of dialysis critically diminish the immune response to HEVAC B. Multiple vaccine injections and maintenance of a minimum anti HBs titre ≥ 20 mIU/ml appear to be the most effective means of eradicating HBV infection from dialysis centres.

Introduction

Hepatitis B virus (HBs) infections represent a major health problem in haemodialysis units. Dialysed patients infected by hepatitis B usually develop mild asymptomatic infections but most of them become chronic carriers of the virus and remain highly infectious [1]. Prevention of hepatitis B infections in such settings is a major goal. The efficacy of hepatitis B vaccine (HEVAC B) manufactured by Institut Pasteur Production has been well demonstrated in healthy individuals. However, in dialysis patients the immune response to the vaccine is poor for any hepatitis B vaccine [2].

We report here the results of a vaccination schedule in which injections of HEVAC B and of hepatitis B immune globulin (HBIg) were repeated in the dialysis patients in our centre until an active anti HBs response could be demonstrated.

Material and methods

HEVAC B vaccine

The vaccine was prepared by Institut Pasteur Production from the plasma of asymptomatic chronic HBs antigen carriers in whom aminotransferase values were normal and HBe antigen was undetectable. Each 1ml vaccine dose contains 5 μ g of HBs antigen [3].

Hepatitis B immune globulins (HBIG)

Hepatitis B immune globulins were prepared by the Lyons Blood transfusion centre from the plasma of blood donors, selected on the basis of an anti HBs titre >5 IU/ml. Each 4ml vial contains more than 100 IU/ml.

Selection of patients

From December 1981 to April 1984, 39 patients dialysed at our hospital in Mâcon were enrolled into this study. There were 25 men and 14 women. Their mean age was 59 years and only three patients were under 40. Twenty-six were haemodialysis patients. Eleven were continuous ambulatory peritoneal dialysis (CAPD) patients, and two patients were changed from CAPD to haemodialysis during vaccination. All patients included in this study were free from serological markers for HBs and had normal aminotransferase values.

Vaccination protocol (Figure 1)

Both HBIG and HEVAC B injections were monitored according to the anti HBs titre on follow-up testing.

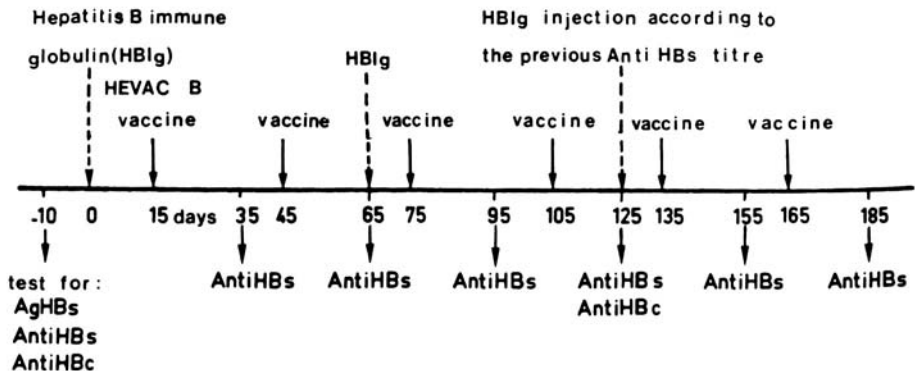


Figure 1. Sero-vaccination protocol and laboratory follow-up

1. HBIg was always given 15 days before the first vaccine dose. Additional doses were administered only in the absence of an active anti HBs response and whenever the residual anti HBs titre fell to <10mIU/ml.
2. HEVAC B vaccine injections were repeated monthly until an HBs antigen appeared. Decision to repeat the injections of HEVAC B depended upon the results of the monthly anti HBs determination.

Follow-up and laboratory procedures (Figure 1)

HBs Ag, anti HBs and anti HBc were tested regularly by radioimmunoassay (Abbott). Serum aminotransferases were tested every three months.

Criteria of active antibody response

Active anti HBs response to HEVAC B was defined as an anti HBs titre >66mIU/ml, 33mIU/ml, or 8mIU/ml respectively found 30, 60 or 120 days after the last injection of HBIg. These levels of anti HBs exceed by 20 per cent the maximal residual levels of passively transmitted anti HBs in dialysis patients [4,5].

Results

No side effects to the vaccine were reported. After four vaccine injections, 44 per cent of patients responded, this proportion increasing progressively to 74 per cent after eight injections and reached 90 per cent following 14 vaccine injections (Figure 2). The antibody response occurred earlier in women than in men. The number of vaccine doses necessary to obtain an immune response increased both with age and with the number of years on dialysis therapy prior to vaccination (Table I).

The mean age of vaccine responders among CAPD patients was higher than among haemodialysis patients for an equal number of vaccine doses, suggesting a better immune response to the vaccine in patients treated by CAPD.

All 11 CAPD patients responded within the first six doses but two CAPD patients failed to respond to the vaccine after 14 vaccine doses. The first patient was receiving radiotherapy and chemotherapy for treatment of a malignant lymphoma discovered during vaccination. The second patient suffered from 14 recurrent peritonitis episodes over three years of CAPD therapy probably as a result of impaired immune responses. Two cases of hepatitis B were observed during follow-up. Patient one was probably contaminated in another centre before coming to our unit since hepatitis B was diagnosed at the time of the second injection (2 months). Patient two was considered as a vaccine responder

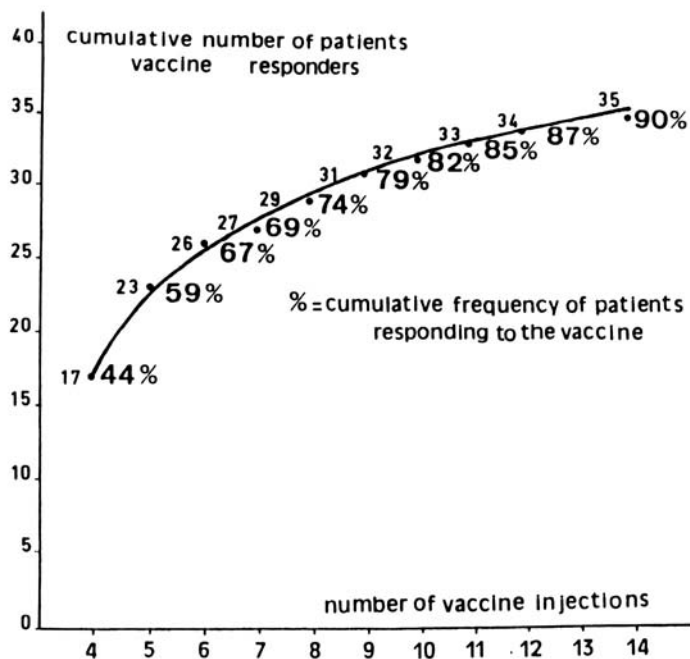


Figure 2. Relation between number of vaccine injections and percentage of vaccine responders among all patients

TABLE I. Influence of age and duration of dialysis therapy prior to sero-vaccination on the immune response in haemodialysis patients and CAPD patients

Responders following to	Haemodialysis patients Vaccine responders			CAPD patients Vaccine responders		
	Mean age (years)	Dialysis duration prior to vaccine (months)	Number of patients	Mean age (years)	Dialysis duration prior to vaccine (months)	Number of patients
4 vaccines	49.5 (27-64)*	8.4 (0-25)*	7	64.6 (47.5-77)*	8.3 (0-23)*	6
5 vaccines	48.5 (42-56.5)	17 (0-35)*	3	75.3 (71.5-80.5)	12.3 (0-25)*	3
6 vaccines	53.5 (47-60)*	33.5 (27-40)*	2	75	0	1
7 and more than 7 vaccines mean=10	60.9 (50-72.5)*	39.6 (21-81)*	7			

on the basis of an anti HBs level ≥ 10 mIU/ml detected 80 days after the fourth vaccine injection and 120 days after the last HBIg injection and so vaccination was interrupted. Hepatitis B occurred five months later.

In 1981, seven patients were chronic HBs Ag carriers, three of them died, two were transferred to other dialysis units and one received a renal transplant. In 1984 there were only two chronic HBs Ag carriers remaining in our centre.

Discussion

The small proportion of vaccine responders (44%) after four vaccine injections can be explained by their advanced age and long duration of dialysis therapy prior to vaccination. The unfavourable effect of age has previously been noted in well documented studies [2,6,7].

Patients with chronic renal failure even when treated by dialysis have a cellular immunodeficiency [8] which certainly contributes to the poor anti HBs response to HEVAC B. As suggested by Rottembourg et al, we recommend that vaccination should be performed in all uraemic patients before they reach end-stage renal failure. However if dialysis has to be started in any susceptible patient, vaccination should be initiated immediately and HEVAC B vaccine injections repeated until active protective anti HBs titres can be obtained. In terms of immunogenicity the results of our vaccination programme are most encouraging. Other intensive vaccination programmes using different hepatitis B vaccines have also been found to improve the immune response in dialysis centres [6,9].

On the basis of this study we offer the following vaccination protocol for all patients with chronic renal failure.

1. Repetition of monthly HEVAC B injection (1 ml) till an anti HBs response can be demonstrated for patients under 40 years and a 2 ml vaccine dose for patients over 40 years.
2. Maintenance of passive protection with parallel HBIg injections.
- 3 Careful monitoring of anti HBs titres should be performed. Booster vaccine doses should be injected regularly to maintain a permanent protective anti HBs titre ≥ 10 mIU/ml and ideally ≥ 20 mIU/ml. Such a permanent protective anti HBs titre will prevent all hepatitis B cases which may occur in the patients who may lose their anti HBs as described by Stevens et al [10]. Eradication of hepatitis B virus infection from dialysis units is feasible and should be obtained with such vaccination programmes.

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