Seroconversion after hepatitis B vaccination in healthy young adults, and the effect of a booster dose

Jennifer Perera¹, Bernadene Perera², and Siritilak Gamage³

(Index words: Anti-HBs titres, non-responders, hypo-responders)

Abstract

Objective Previous studies have shown that 5% to 15% of healthy people do not show a protective antibody response following hepatitis B vaccination. The study was done to determine the protective efficacy of vaccination in healthy young adults 1 to 4 years after the three dose vaccination series and to study the effect of a booster dose on non-responders and hypo-responders.

Design Prospective intervention study.

Setting From January to June 2000, Faculty of Medicine, University of Colombo.

Study group 258 volunteers from five batches of medical students vaccinated with three doses of the recombinant vaccine at 0, 1 and 6 months.

Results 9.5% were non-responders. Duration of vaccination, sex and body mass index were not significantly associated with anti-HBs levels. 28.6% of non-responders developed protective anti-HBs titres after a booster dose. The persistent non-responders did not have a chronic illness or past HBV infection.

Conclusions A substantial number do not seroconvert after hepatitis B vaccination. Testing of blood for anti-HBs one month after vaccination is recommended to recognise non-responders as a booster dose will be beneficial in the majority of them.

Introduction

The discovery of the aetiologic agent of hepatitis B (HB) and the development of safe and effective vaccines is one of the remarkable achievements of the 20th century. HB is transmitted by percutaneous or permucosal exposure to infectious body fluids, by sexual contact with an infected person and perinatally from an infected mother to her infant. The consequences of acute hepatitis B virus (HBV) infection are variable. Newborn babies are generally asymptomatic and the typical illness is seen in only 5 to 15% of children 1 to 5 years of age (1). Older children and adults are symptomatic in 33 to 50% of infections. Fulminant hepatitis occurs in 1 to 2% of people with acute disease, which has a case fatality rate of 63 to 93%.

Chronic HBV infection is defined as the presence of HBsAg in serum for at least 6 months. The risk of developing chronic infection is highest for infants (about 90%) infected in the perinatal period, compared to 6 to 10% of acutely infected adults (2). 15% of adolescents and young adults with chronic HBV infection are at substantially increased risk of developing chronic liver disease, including cirrhosis of the liver and hepatocellular carcinoma.

In Sri Lanka epidemiological surveys of the community and in blood donors show that the prevalence of chronic HBV infection is low, ranging between 0.7 and 2.5% (3). A survey in 1996 showed a prevalence of 0.15% among all categories of health care workers (3/2000) and 0.5% in medical officers (1/206) (4). A study of 456 medical students before exposure to clinical work showed a prevalence of 0.44% (5).

Vaccination of individuals at risk of exposure to HBV has been the main method of controlling the morbidity and mortality associated with HBV. The recommended schedule of vaccination of healthy subjects consists of three doses at 0, 1 and 6 months. The protective efficacy of HB vaccination is directly related to the development of anti-HBs antibodies. Those who develop anti-HBs titres of >10 mIU/ml after a primary vaccination series are protected against clinical illness and chronic infection (6). Studies of the antibody response to currently licensed plasma derived hepatitis B vaccines and hepatitis B vaccines prepared by recombinant technology have shown that between 5 to 10% or more of healthy people do not show an anti-HBs antibody response to the surface antigen component (HBsAg) of these preparations (non-responders), or respond poorly (hypo-responders) (7), conditions that are defined as showing less than 10 mIU/ml and 10 to 100 mIU/ml of anti-HBs respectively against an international antibody standard. Non-responders remain susceptible to infection with HBV.

The recommended series of three intramuscular doses of HBV vaccine induces a protective antibody response in over 90% of healthy adults below 40 years of age. By the age of 60 years only 75% of people vaccinated develop protective levels of anti-HBs (8). Host factors such as smoking, obesity, immunosuppression, past HBV infection, of immune deficiency disorders and chronic illnesses adversely affect the antibody response.

Methods

Study group

The study was conducted at the Faculty of Medicine, Colombo from January to June 2000. The study popul-
Papers

The population comprised 258 medical students who had been vaccinated with three doses of the recombinant vaccine intramuscularly to the deltoid region at 0, 1 and 6 months.

**Study design**

Blood samples from the study group were tested for anti-HBs titre using a quantitative enzyme linked immunosorbent assay (ELISA) by Abbot-Murex. Data on factors known to affect seroconversion were obtained using a self-administered questionnaire. The data included sex, age, body weight and height, duration after vaccination, presence of a chronic disease such as diabetes and other immune deficiency states.

The risk of infection with HBV was also assessed from a history of needle pricks, family or close contact with a chronic carrier of HBV and sexual contact.

In the second phase of the study, participants who did not have protective antibody levels (non-responders, anti-HBs less than 10 mIU/ml) and hypo-responders (anti-HBs less than 100 mIU/ml) were given a booster dose of the vaccine and retested after one month for seroconversion or a rise in the anti-HBs antibody titre. Participants who did not seroconvert after this were investigated further by an interview to probe their past medical history and by testing for serological evidence (anti-HB core antibody) of past HBV infection.

**Results**

The participants were from 13 districts of the island, and the percentages were, Colombo 58.2, Gampaha 15.5, Kalutara 8.8, Kegalle 3.6, Matara 3.6, Galle 2.8, Kurunegala 2.4, Ratnapura 2.0, Hambantota 0.8, Puttalam 0.4, Nuwara Eliya 0.4 and Badulla 0.4. The numbers of volunteers from the five batches of students and the duration after vaccination are shown in Table 1. 90.3% (223/258) showed a protective antibody response (anti-HBs >10 mIU/ml) following vaccination. 9.5% were non-responders. The majority (54%) showed a good antibody response (>100 mIU/ml) against HBV infection. Table 2 shows the anti-HBs titres in relation to duration of vaccination. In our study there was no significant association between the anti-HBs titre and duration after vaccination which varied from 12 to 40 months. Sex and body mass index were not significantly associated with seroconversion. Type of vaccine, dose and route of vaccination were not significant variables.

In the study population 64 gave a history of accidental needle pricks, 2 had close contact with a chronic hepatitis B patient, and 8 had had homosexual or heterosexual intercourse. Hence 28.6% had a potential risk factor for acquiring HBV infection.

Among the 26 non-responders (anti-HBs <10 mIU/ml), 22 volunteered for retesting after a booster dose of HB vaccine. Among the 103 hypo-responders 12 who had anti-HBs titres of 10-100 mIU/ml were retested after a booster dose. All hypo-responders developed anti-HBs titres over 100 mIU/ml. Among the 22 initial non-responders, 3 (13.6%) continued to be negative for anti-HBs antibodies, but did not have any identifiable chronic illness and tested negative for anti-HB core (HBc) antibodies indicating absence of past HBV infection.

**Table 1. Number of student volunteers from each batch and duration after vaccination**

<table>
<thead>
<tr>
<th>Batch</th>
<th>Number studied</th>
<th>Duration after vaccination (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992/93</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>1993/94</td>
<td>68</td>
<td>28</td>
</tr>
<tr>
<td>1994/95</td>
<td>51</td>
<td>28</td>
</tr>
<tr>
<td>1995/96</td>
<td>49</td>
<td>12</td>
</tr>
<tr>
<td>1996/97</td>
<td>52</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>258</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Anti-HBs antibody levels and duration after vaccination**

<table>
<thead>
<tr>
<th>Duration after the third dose (months)</th>
<th>Number of non-responders (%)</th>
<th>Responders and anti-HBs titres in mIU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10-100 (%)</td>
</tr>
<tr>
<td>40 (n = 38)</td>
<td>3 (7.9)</td>
<td>9 (23.7)</td>
</tr>
<tr>
<td>28 (n = 119)</td>
<td>11 (9.2)</td>
<td>51 (42.8)</td>
</tr>
<tr>
<td>12 (n = 101)</td>
<td>12 (11.5)</td>
<td>43 (42.5)</td>
</tr>
<tr>
<td><strong>Total (n = 258)</strong></td>
<td><strong>26 (9.5)</strong></td>
<td><strong>103 (36.3)</strong></td>
</tr>
</tbody>
</table>
Discussion

The minimum protective level of anti-HBs following immunisation has been set in protective efficacy studies at 10 mIU/ml. The titre required for protection against particular routes of infection and the size of the inoculum may vary. For example, a follow up study of vaccinated homosexual men reported an overall incidence of HBV infection of 2.9 per 100 person years, with nearly 75% occurring in people with an anti-HBs titre less than 10 mIU/ml at the time of infection, and in only a few with anti-HBs titres over 50 mIU/ml (10). A much lower asymptomatic HBV infection rate of 0.8 per 100 person years was observed after immunisation of health care workers in nephrology units who had antibody titres less than 50 mIU/ml (11).

Vaccine induced anti-HBs titres are highest one month after booster vaccination, but decline rapidly during the next 12 months and thereafter more slowly (6).

Providing booster vaccination to all vaccinated subjects at regular intervals without determination of anti-HBs is not supported by evidence (15,16). Testing of the antibody level one month after the last dose of vaccination is recommended to identify non-responders and hypo-responders (16,17). Numerous studies indicate that administration of four, five, six or more doses of the vaccine in non-responders or hypo-responders results in production of protective levels of anti-HBs in about 50% (12,13,14,15). In our study a booster dose of the vaccine resulted in 86% of non-responders developing protective anti-HBs levels.

The European Consensus Group on hepatitis B immunisation recommends the following for health care workers and others at occupational risk who do not develop protective anti-HBs titres after the initial vaccination series (16): screen for markers of present or past HBV infection (HbsAg, anti-HBc); administer an additional booster dose of the vaccine, repeat anti-HBs measurement; consider passive immunisation with HB immunoglobulin following exposure.

The US Public Health Service Guidelines for the management of occupational exposures to HBV recommends that people who do not respond to the primary vaccine series be given a second 3-dose series as there is a 30 to 50% chance of responding to the latter (17).

Acknowledgements

We are grateful to the medical students who participated in the study, the University of Colombo for financial assistance, Drs Thushara Amarasinghe, Nishadi Ranasinge, Chandrika Ponnampuruma, Anuja Ponnampuruma, Samantha Jayamaha and Shivantha Fernandopulle for collection of blood, Ms Shirani Hendalage for secretarial assistance, and Mr P G Ratnasereka for laboratory assistance.

References


