Hepatitis B vaccine immunoresponsiveness in adolescents: a revaccination proposal after primary vaccination

Juan Simó Miñana,*, Marisol Gaztambide Ganuza, Pilar Fernández Millán and Marina Peña Fernández

Hepatitis B recombinant vaccine immunoresponsiveness was studied in 427 preadolescents vaccinated with a 0, 1 and 6 months vaccination schedule. AntiHBs postvaccination titres (measured one month after the last dose) were related to the following variables: sex, weight, height and Quetelet index. The antiHBs postvaccination titres were used to predict the length of protection induced by the vaccine. All preadolescents developed antiHBs titres 10 IU l−1 and no statistically significant differences could be found between sexes. The relation study between antiHBs postvaccination levels and Quetelet index showed a statistically significant inverse correlation. According to the antiHBs postvaccination titres, the central 50% of the sample distribution would be protected during a period between 7.5 and 10.5 years. In pre-teenagers, the hepatitis B recombinant vaccine has proven to be highly immunogenic, obesity is a predictor of poor immunoresponse and this response is not influenced by sex. According to our results, we would propose the administration of a single booster dose 10 years after primary vaccination and thus protect these subjects during the period of greatest risk.

Keywords: Hepatitis B vaccine; immunoresponsiveness; adolescents

The prevention of hepatitis B virus (HBV) infections is one of the most important public health problems. The HBV carriers are the main reservoir of the virus. The risk of chronic HBV infection is greatly increased when acute infection takes place at an early age. Spain is a country where 70% of HBV infections occur before the age of 30, with a medium to low HBV chronic carriers prevalence (1–2%).

The low cost and unlimited availability of the recombinant vaccine make it possible to contemplate the eradication of hepatitis B and thus, initiatives for the universal vaccination of newborns and adolescents are being introduced in several countries including Spain. The vaccine’s length of protection is still not clearly defined and the revaccination period has not been precisely set. The factors associated with poor immune response to the hepatitis B vaccine in healthy persons are sex, age, obesity and buttock injection.

This study involves the monitoring of anti-hepatitis B vaccine immunoresponsiveness in a sample of preadolescents after the implementation of a universal vaccination programme. Immunoresponsiveness was then related to other variables (sex, weight, height and Quetelet index).

The other objective of the study was to predict the length of protection induced by the vaccine based on the antiHBs postvaccination titres reached one month after concluding a 0, 1 and 6 months vaccination schedule.

Participants and Methods

A universal vaccination programme for 12-year-old preadolescents was initiated in Elche (Spain) in October, 1992. Elche is a small city of 200 000 inhabitants and with 53 primary schools. The vaccine used in this programme was the recombinant hepatitis B vaccine Engerix B® (SKF), with three 20 μg doses administered in the deltoid region following a 0, 1 and 6 month vaccination schedule. The target population of the programme was all of the 12-year-old schoolchildren (3348) of this city. A random sample of 432 properly vaccinated children was selected from all of the local primary schools in Elche.

Initially, all of the members of this sample were screened for antiHBc (marker of infection). Only those found to be antiHBc positive were then screened for HBsAg. All children positive for antiHBc were excluded from the study. All of the members of the sample were weighted and their height recorded at the moment the
blood test was performed. Serum levels of antiHBs were measured in all children one month after the last dose. The presence of antiHBs was detected by solid-phase radioimmunoassay (AUSAB, Abbott Laboratories). Titres 10 IU l-1 were considered to be the protective levels of antiHBs.

At this point, it is necessary to clarify that antiHBs levels were measured quantitatively up to 100 000 IU l-1 and upper level titres were determined qualitatively and expressed as 100 000 IU l-1; however, a normal antiHBs distribution curve was not observed among the subjects of our sample (Kolmogorov-Smirnov test). Based on these two considerations, non-parametric tests (Mann-Whitney U test and Spearman Correlation) were used in the statistical analysis.

A relationship was sought between the antiHBs postvaccination level variable and each of the following variables: weight; height; and Quetelet index. The Spearman Correlation test was applied in order to study this relationship. The Quetelet index (weight/height index) was chosen as a surrogate measure of obesity and was computed as follows: weight (kg)/height (m)². The Mann-Whitney U test was used to compare antiHBs postvaccination titres between male and female and obese and non-obese members sample. The subjects were considered as obese persons if their Quetelet index was over the 90th percentile.

An attempt was made to predict the length of protection induced by the vaccine based on the antiHBs titres reached and measured one month after the last dose. This was possible with the aid of a table developed by Ambrosch et al. These researchers designed a table (Table 1) as instrument for estimating the persistence (measured in months) of vaccine-induced antiHBs, based on the initial antiHBs titres determined one month after the last dose of the vaccine.

RESULTS

Five of 432 children (1.15%) were antiHBc positive and one of the five was HBsAg positive. These five children were excluded from the immunoresponsiveness study. The final sample was made up of 427 children of which 47% were male and 53% were female.

The immunoresponsiveness results are outlined in Table 2. It is important to note that all children developed titres 10 IU l-1, which indicates that 100% serous protection was achieved. The distribution median for antiHBs postvaccination titres of the sample was 36.520 IU l-1 (CI: (30 680, 43 210); a=0.05), which means that 50% of the subjects sample would be protected for 9 years or more. It is also important to note the high percentage of children who obtained titres 2 100 000 IU l-1 (20.15%), which would imply a protection period of over 130 months (11 years or more); and that 72% of the children developed titres 2 16 000 IU l-1 which would imply a protection period of over 98 months (8 years or more).

The interquartilic interval (interquartile range from 25th percentile to 75th percentile) of the antiHBs titres distribution for the sample was situated between these titres (13 010-80 920 IU l-1). This means that the central 50% of our sample distribution would be protected during a period between 90 and 125 months (between 7.5 and 10.5 years).

The Spearman Correlation test yielded correlation coefficients for the antiHBs postvaccination level

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<th>AntiHBs level postvaccination (IU l-1)</th>
<th>Length of protection (in months)</th>
<th>n</th>
<th>%</th>
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variable with respect to the weight, height and Quetelet index variables, respectively. The correlation index between antiHBs postvaccination level and the Quetelet index was the one that diverged most from zero ($r = -0.118$) and the only one which was statistically significant ($P = 0.015$).

The Mann–Whitney $U$ test was used to compare antiHBs postvaccination titres between males (distribution median=37740 IU $1^{-1}$) and females (distribution median=36010 IU $1^{-1}$); no statistically significant differences could be found ($P = 0.05$). The same test was used to compare antiHBs postvaccination titres between obese subjects (distribution median=34 186 IU $1^{-1}$) and non-obese subjects (distribution median=47 186 IU $1^{-1}$); the differences were statistically significant ($P = 0.01$).

**DISCUSSION**

Our results indicated that 100% of the children responded satisfactorily to the vaccine, all of them achieved antiHBs levels 10 IU $1^{-1}$. More than 20% of the children responded very satisfactorily and their antiHBs postvaccination titres exceeded 100 000 IU $1^{-1}$. These results lead us to consider that the HBV recombinant DNA vaccine is highly immunogenic when administered to pre-teens. Furthermore, our results indicate that obesity is a predictor of poor antibody response to the hepatitis B vaccine, this conclusion is in line with observations made by other researchers. Some published trials have associated the female sex with poor immunogenic response, while other studies yielded poor response in males. In most cases, these differences have not been statistically significant. In the present study, no significant differences were observed between the sexes when comparing antiHBs postvaccination levels.

The persistence of the antiHBs titres after vaccination has been investigated in several trials. The maximum antiHBs level is reached between 1 and 2 months after the last vaccine dose and from that moment on, the antiHBs level begins to decrease. The fall in antiHBs level is rapid at first (during 20–24 months), but subsequently, the fall is slower. At present, the vaccine length of protection is considered to be related to the maximum level of antiHBs attained after vaccination. This relationship has been amply dealt with in several studies and is included in Table 1. The development of this table was based on data from prospective studies which were carried out on properly vaccinated healthy adults. In view of a small number of studies of this type made with children, we decided to use this table in our study.

There is still uncertainty about the persistence of the vaccine-induced protection, the need for revaccination and thus, the scheduling of the revaccination. Most of the previously vaccinated subjects whose antiHBs titres had decreased to low or even undetectable levels have been observed to have a rapid anamnestic response to a single booster dose of the vaccine, thus indicating the persistence of immunologic memory. Although there is at present strong evidence indicating that the immunologic memory achieved by the hepatitis B vaccination is capable of protecting against disease for at least a few years after antiHBs postvaccination titres become undetectables, some researchers suggest that continued surveillance is needed in order to fully evaluate this hypothesis, particularly in cases where the population has been immunized at birth or during infancy. For this reason, other authors do not claim, for the moment, that booster doses are unnecessary. Follow-up studies of vaccinated persons have identified a number of HBV infections in subjects that had responded to hepatitis B vaccine. The vast majority of these infections, however, were characterized only by being antiHBc positive, while no HBsAg was detected and no hepatitis symptoms were reported. As a result, other sources insist that a longer follow-up of immunized subjects is necessary to determine the necessary procedures; until this is feasible and for the time being, there is no reason for recommending booster vaccinations as a public health measure.

With respect to the persistence of vaccine protection, perhaps the most important data compiled in the present study involve the interquartile interval obtained. This indicates that the central 50% of our sample distribution would be protected (in accordance with the Ambrosch table) from 7.5 to 10.5 years.

In areas of low–medium endemicity, most HBV infections occur in teenagers and young adults. A potential problem with the universal vaccination of pre-teenagers against HBV in these areas is that the vaccine induced antibody would have decreased to relatively low levels by the time the period of the greatest risk was reached. Although the recombinant vaccine has proven to be highly immunogenic in preadolescents, and in line with our results, we propose the administration of a single booster dose 10 years after the last dose of primary vaccination and thus, protect these children during the period of greatest risk.

Nevertheless, it will be necessary to perform long-term monitoring studies in order to fully evaluate the duration of the vaccine-induced protection against the illness and its acute complications, as well as the effects on the condition of the chronic HBV carrier. We are of the opinion that these studies are all the more necessary in the case of the vaccination of newborn babies, children and adolescents.

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**REFERENCES**

6. Ramón Torrell, J.M., Micheo Salas, C., Cerdó Goicou, C., Casas García, I., and Escrivá Jordana, J.M. Respuesta...
inmunogenicity of hepatitis B vaccines in adolescents: J. Simó Miñana et al.


5. Sheirman, N., Gesman, M., Maurer, C., Just, M. and Berger, R. Persistence of antibodies after immunization with a recombinant yeast-derived hepatitis B vaccine following two different schedules. Vaccine 1990, 8 (Suppl.), 44–45


