HEPATITIS B VIRUS VACCINE RESPONSE IN CHILDREN 15–19 YEARS OLD

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ABSTRACT
To determine Hepatitis B virus vaccine response in vaccinated children 15 – 19 years old. Three hundred children were vaccinated after an informed consent and after tests for Hepatitis B virus (HBV) markers (HBsAg, anti-HBc and anti-HBs) during 1999 – 2000 in program INTERREG II of European Community (EC). All of them were negative before vaccination. The children were vaccinated by the classic (months 0, 1 and 6) schedule (XI, XII 1999 – V 2000). Recombinant Hepatitis B vaccine ENGERIX™ (SmithKline Beecham Biologicals S.A. – Belgium) was given as 20 mcg intramuscular injections via the deltoid muscle. Seroconversion was defined in 280 of them on days 30 or more after the last immunization as the presence of hepatitis B surface antibody concentration >= 10 IU/L in serum samples, while concentrations of >=100 IU/L were considered to be seroprotective. The serological hepatitis B surface antibody titration was carried out using a commercial ELISA kits (DiaSorin – ETI – AB – AUK – 3 – Italy) and DiaSorin automated system and software. After three doses of vaccine, anti HBs concentration reached levels >=10 IU/L was determined in 96.3% of children. Protective levels >= 100 IU/L was determined in 86% of them. The initial immune response to hepatitis B vaccine following the basic immunization series is an important determinant of the duration of immunity. Our data indicate that performed Hepatitis B vaccine induced good immune response of the children vaccinated, but 3.6% of them failed to produce any antibody response and 10.3% failed to produce protective antibody levels. For the last children a booster doses of vaccine must be applied.

Introduction
Hepatitis B virus (HBV) infection is a common viral disease, which constitutes a serious health issue throughout the world due to its morbidity, mortality and economical losses. World Health Organization (WHO) has recently estimated about 367 million carriers of HBV, many of them will develop chronic liver diseases including cirrhosis and primary hepatocellular cancer (14). Immunization against HBV, introduced about 20 years ago, has made this infection a vaccine preventable infectious disease. The objectives of vaccination are primarily to prevent infection, thereby reducing the incidence of persistent HBV infection and chronic liver disease, and in addition eliminating the pool of chronic carriers, thus limiting transmission of infection to susceptible contacts (2). Clinical trials have demonstrated the safety and efficacy of the currently licensed HBV vaccine (6). Immunization studies with normal hosts showed good response by classic schedule (11). All studies of the antibody response have shown that between 5% and 15% or more of healthy immunocompetent subjects do not mount an antibody response to the surface antigen (HBsAg) component present in these preparations (17).

The aim of this study was to determine recombinant Hepatitis B ENGERIX™ (SmithKline Beecham Biologicals S.A. – Belgium) vaccine response in vaccinated children 15 – 19 years old.
Materials and Methods

Three hundred children were vaccinated after an informed consent and after tests for HBV markers (HBsAg, anti-HBc and anti-HBs) during 1999 – 2000 in program INTERREG II of European Union (EU). All of them were negative before vaccination. The children were vaccinated by the classic (months 0, 1 and 6) schedule (XI., XII.1999 and V.2000). Recombinant Hepatitis B vaccine ENGERIX™ (Smith-Kline Beecham Biologicals S.A. – Belgium) was given as 20 mcg intramuscular injections via the deltoid muscle. Seroconversion was defined of 280 of them, in serum samples, collected on days 30 or more after the last immunization.

Serological methods: The serological hepatitis B surface antibody titration was carried out using a commercial ELISA kits (DiaSorin – ETI – AB – AUK – 3 – Italy) and DiaSorin automated system and software. The presence of hepatitis B surface antibody (anti-HBs) concentration >=10 IU/L was indicative of positive response to vaccination, while concentration >=100 IU/L was considered to be seroprotective.

Results and Discussion

An ELISA (Table) revealed the presence of anti-HBs concentration at >=10 IU/L in 270 children (96.3%), with the anti-HBs concentration being equal or higher than 100 IU/L in 241 (86%) of them (good responders), between 10 IU/L and 99 IU/L in 29 (10.3%) of them (poor responders), and lower than 10 IU/L in 10 (3.6%) of them (non-responders). Mean anti-HBs concentration rate was 8173.455 IU/L. No significant HBV vaccination-related adverse effects were seen in any of the children.

In our study the performed Hepatitis B vaccine ENGERIX™ (SmithKline Beecham Biologicals S.A. – Belgium) is genetically engineered hepatitis B vaccine derived from yeast. Active ingredient is Hepatitis B surface antigen (HBsAg, recombinant).

<table>
<thead>
<tr>
<th>Anti HBs concentration (mean rate)</th>
<th>n</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>&lt; 10 IU/L</td>
<td>10</td>
<td>3.6</td>
</tr>
<tr>
<td>10 - 99 IU/L (66.85)</td>
<td>29</td>
<td>10.3</td>
</tr>
<tr>
<td>100 - 999 IU/L (456.27)</td>
<td>120</td>
<td>42.8</td>
</tr>
<tr>
<td>&gt;= 1000 IU/L (17225.23)</td>
<td>121</td>
<td>43.2</td>
</tr>
<tr>
<td>Total</td>
<td>280</td>
<td>100</td>
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Conventionally (2), a primary vaccine course consists of three doses, the first and second being separated by a month, and the third being given approximately 6 months after the first. The first two doses usually suffice to initiate the production of antibodies against the HBsAg (anti-HBs), thereby priming the immune system for a second response. The third dose stimulates this secondary response, resulting in anti-HBs concentrations being higher than after the first two doses; anti-HBs develop more rapidly after the third dose.

Immune responsiveness to HBV vaccine should be documented 1 to 2 months after completion of the vaccination protocol (3). In our study postvaccination anti-HBs testing to confirm response to vaccination was performed 30 or more days after the 3rd immunization. Presence of anti-HBs at concentration >=10 IU/L was detected in 270 children (96.3%). All studies of the antibody response to currently licensed hepatitis B vaccines have shown that between 5% and 15% or more of healthy immunocompetent subjects do not mount an antibody response to the surface antigen (HBs Ag) component present in these preparations (17). The exact proportion depends partly on the definition of non-responsive or poor-responsive, generally <10 IU/L or <100 IU/L respectively, against international antibody status (18). Levels above 100 IU/L were considered as effective (15). In our study the anti-HBs titer being equal or higher than 100 IU/L in 241 (86%) of the children vaccinated (good
responders), between 10 IU/L and 99 IU/L in 29 (10.3%) of them (poor responders). Baldy et al. (1) reported that 81.5% of individuals had become anti-HBs positive and 65.5% of them were a good responders. Idilman et al. (5), Ul Haq et al. (12), Levie et al. (7) found immune response in 92%, 96.3% and 99% in healthy young adults 15-40 years old respectively.

In our study anti-HBs antibody concentration lower than 10 IU/L was found in 10 (3.6%) of the children vaccinated (non-responders). Data et al. (3) reported that non-responders should be revaccinated with the full 3-dose series. If the anti-HBs concentration is less than 10 IU/L after 2 complete HBV vaccine series have been administered, the person is considered a nonresponsive, and therefore susceptible to infection with HBV. A few articles have been reported on patients with underlying immunological disorders, who fail to produce protective antibody levels. Non-responders remain susceptible to infection with HBV. Several factors adversely affect the antibody response to HBs including the site and route of infection, gender, advancing age, increasing body mass index, immunosuppression and immunodeficiency. The response to the vaccination decreased with increasing age (9, 16). Protection from non-cytopathic viruses is dependent on a complex interplay between the role of memory B cells, memory T-helper cells, memory cytotoxic T lymphocytes and antigen-antibody complexes. Although neutralizing antibodies to the HBsAg conventionally measured by anti-HBs response in commercial kits, are required for HBV clearance. Genetic factors affect anti-HBs response after vaccination (4, 8, 10, 13). Lemon et al. (6) reported that postvaccination anti-HBs testing to confirm response to vaccination was not commonly practiced, but anti-HBs correlate with protection. The initial immune response to HBV vaccines following the basic immunization series is an important determinant of the duration of immunity.

In conclusion, immunization of susceptible persons against HBV is necessary to prevent not only acute disease but also the carrier and chronic states of HBV infection. The vaccine ENGERIX™ (SmithKline Beecham Biologicals S.A. – Belgium) used in this study was shown to be safe, well tolerated and highly immunogenic. As all volunteers recruited in our study belonged to a young age group and were considered healthy, a relatively high vaccine response rate was observed. A small number of slow or non-responders were detected. For the last children booster doses of vaccine must be applied. Worldwide use of hepatitis B vaccines for the newborn, young children and high-risk groups controls this infection and obviates the need for vaccine against hepatitis D.

REFERENCES