Immunogenicity of a low-cost hepatitis B vaccine in the South African Expanded Programme on Immunisation

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Background. A low-cost, 'flash' heat-inactivated hepatitis B vaccine with enhanced immunogenicity allowing for a relatively low dose (Hepaccine B; Cheil Foods and Chemicals, Korea) was introduced into the South African Expanded Programme on Immunisation during 1995 to immunise infants against hepatitis B. To determine the seroresponse of this vaccine in South Africa, a country with a high hepatitis B virus (HBV) prevalence, a field trial was conducted in a rural health clinic.

Methods. The immunogenicity of Hepaccine B, containing 1.5 µg/0.5 ml, was studied in 186 black infants attending the Soshanguve III clinic, north-west of Pretoria. Infants receiving three consecutive doses in the anterolateral thigh at 6, 10 and 14 weeks were monitored. The doses were administered concurrently with their routine oral polio vaccine (OPV) and diphtheria, pertussis and tetanus (DPT) immunisations. Vaccine side-effects were recorded. Blood specimens were collected 3 months after the final vaccination. Sera were tested for antibodies to hepatitis B surface antigen (anti-HBs) by IMx AUSAB (Abbott Laboratories, USA). Levels of anti-HBs were determined by comparison with standard reference preparations and expressed in mIU/ml.

Results. Side-effects of the vaccine were minor, with limited local reaction at the site of administration. The anti-HBs seroconversion rate was 93.0%, based on a titre of $\geqslant$ 10 mIU/ml with a geometric mean titre of 257.58 mIU/ml.

Conclusions. Administration of 1.5 µg doses of Hepaccine B at 6, 10 and 14 weeks is safe and highly immunogenic in black South African infants, and this vaccine is suitable for use in countries with high HBV prevalences such as in Africa. The use of an economical hepatitis B vaccine would greatly facilitate the prevention of hepatitis B in these countries.

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Hepatitis B virus (HBV) infection is a serious public health problem for many countries in the world. There are currently at least 300 million HBV carriers globally, with an estimated 2 million residing in South Africa. Currently, effective and immunogenic hepatitis B vaccines are available and have brought hope for the prevention of hepatitis B. An effective vaccination programme should take into account the unique local epidemiological pattern, the health care delivery system, and the social and resource implications. Although genetically engineered hepatitis B vaccines are being manufactured, the plasma-derived vaccines are still more economical, especially if manufactured in a country with a high prevalence of carriers. Hepaccine B, the vaccine used in this study, is a multideterminant heat-inactivated hepatitis B vaccine produced from human plasma by Cheil Foods and Chemicals, Korea, based on technology licensed from the New York Blood Center, USA.[1] Currently all plasma-derived hepatitis B vaccines undergo inactivation procedures that eliminate the risk of infection with blood-borne pathogens.[2] The controversy about plasma-derived vaccines arises from the perception that blood-borne diseases such as AIDS could be transmitted through plasma-derived vaccine. Exhaustive tests have shown that this is not possible[3] and respected organisations such as the World Health Organisation have fully endorsed the use of both types of vaccine.[4] The South African Department of Health decided to use a plasma-derived vaccine for two reasons: it was shown to be as safe and effective as the recombinant vaccine, and it was more affordable. Doses of 1.5 µg Hepaccine B in a 0-, 1- and 2-month schedule have been approved for infants. The efficacy of this particular vaccine is not an issue as it has been assessed previously and found acceptable in principle for purchase by United Nations agencies for infant immunisation programmes in developing countries. Recently several reports pointed out the need to evaluate the effectiveness of hepatitis B vaccination regimens used in endemic countries since it cannot be assumed that the manufacturer's recommendations apply to a particular population.[5-7] We report on the adverse event profile associated with administration of 1.5 µg doses of Hepaccine B hepatitis B vaccine at 6, 10 and 14 weeks in black South African babies as well as the good seroresponse to the vaccine 3 months after the last inoculation.

Participants and methods

Study population and immunisation protocol

Approval for the study with a clearance certificate was obtained from the Ethics Committee of the Faculty of Medicine at the Medical University of Southern Africa, as well as from the nursing manager of the Soshanguve clinics. Three hundred and eleven babies attending the Soshanguve III clinic, north-west of Pretoria, were enrolled in the study and 0.5 ml (1.5 µg) injections of Hepaccine B were administered intramuscularly in the right anterolateral thigh at 6, 10 and 14 weeks. No blood was collected from the subjects prior to immunisation. The infants eligible for participation in the study were those who were to receive oral polio virus (OPV) and diphtheria, pertussis and tetanus (DPT) immunisations at 6 weeks. The doses were administered concurrently with their routine OPV and DPT immunisations. The vaccines were administered by the clinic sisters, using 1 ml syringes and 1.5 E-1 needles.

Parental information and consent

The nursing sisters ensured that parents/guardians understood the protocol by explaining in their own language what vaccination is all about, the importance of taking the full course of vaccination and the necessity of post-vaccination blood sampling. Informed consent was explained to parents or guardians of the infants as they were recruited. Those who agreed were requested to sign a consent form prior to the first dose.

Documentation and immunisation monitoring

Each respondent was monitored in respect of name, age, sex, address, birth weight, contact person, dates of vaccination, post-vaccination follow-up and vaccine side-effects. Pink calenders were attached to respondents' Road-to-Health cards on which the date of the next clinic visit was highlighted.

Methods for evaluation of vaccine immunogenicity

Blood samples for post-vaccination testing. Blood was collected from all infants who had received three doses of vaccine, 3 months after the final dose, to test for seroconversion and quantification of antibody levels. Three millilitres of blood were taken from the jugular vein of the respondents by qualified paediatricians at the clinic. Blood samples were kept in a coldbox with ice-packs and transported to the virology laboratory at MEDUNSA, where samples were immediately centrifuged. The serum fractions were stored at –20°C until tested.

Laboratory methods. Quantitated levels of antibodies to hepatitis B surface antigen (anti-HBs) were determined in the stored serum fractions using a microparticle enzyme immunoassay (IMx AUSAB, Abbott Laboratories, USA). The IMx System was calibrated using IMx AUSAB Calibrators (Abbott Laboratories, USA) for each AUSAB reagent pack that was used. The IMx AUSAB Calibrators have the following concentrations of anti-HBs: 0, 10, 50, 100, 500, 1 000 mIU/ml. A positive control, a negative control and a calibrator were run with each set of tests. Levels of anti-HBs were determined by the IMx system in relation to the calibration curve and expressed in mIU/ml. An antibody titre (anti-HBs) of 10 mIU/ml is regarded as the minimum protective concentration against HBV infection[8] and in this study we defined a titre of $\geq$ 10 mIU/ml as seroprotective.

Computerisation and analysis of the results

All data from infants and the quantitated anti-HBs results were entered into a PC using an Excel database spreadsheet. Analysis of results was undertaken with the Excel programme and the use of standard statistical methods.

Results

Characteristics of children given Hepaccine B and compliance rate

The sampling of the children eligible for this study was restricted to consecutive cases arriving on the immunisation clinic days during the time of the study. It was further restricted by the health of the child — parent/guardian consent was not an issue as it was obtained in all cases. No blood was collected prior to vaccination. Out of 311 infants who received the first dose, 254 (81%) returned for their second dose. A total of 229 (73.6%) infants received three doses of Hepaccine B, and 186 returned 3 months later for blood collection.

Serological assays

Table I indicates the immunogenicity of Hepaccine B 3 months after the last dose in 186 infants tested. Although 13 babies had anti-HBs values below 10 mIU/ml, 6 babies were hyporesponders who tested positive by the IMx AUSAB assay with anti-HBs values between 2 and 9.9 mIU/ml. The anti-HBs seroprotective rate based on a titre of ⩾ 10 mIU/ml was 93.0% with the 95% confidence intervals being between 89.3% and 96.7%. The geometric mean titre was 257.58 mIU/ml and the arithmetic mean titre was 580.6 mIU/ml. A slightly higher seroconversion rate was found in girls (95.4%) than in boys (90.9%), but with no significant difference.

Table I. Immunogenicity of Hepaccine B 3 months after last dose, in 186 infants tested (seroprotection ⩾ 10 mIU/ml = 93.0%)

Anti-HBs titre	No. of infants	%
< 10 mIU/ml	13	7
10 - 99.9 mIU/ml	38	20.4
100 - 999.9 mIU/ml	108	58.1
⩾ 1 000 mIU/ml	27	14.5
Geometric mean titre	257.6 mIU/ml	

Side-effects of vaccination

Side-effects of the vaccine were minor, with limited local reaction at the site of administration (Table II).

Table II. Side-effects of Hepaccine B vaccination (% monitored)

	At injection site			
Vaccination	Mild redness and mild swelling	Abscess	Haemorrhagic necrosis	Systemic fever
First	18/253 (7.1%)	None	None	3/253 (1.1%)
Second	18/232 (7.7%)	None	None	1/232 (0.4%)
Third	2/186 (1.1%)	None	None	1/186 (0.5%)

Discussion

The objective of undertaking the exercise detailed in this paper was to ascertain the immunogenicity of Hepaccine B hepatitis B vaccine 3 months after the last dose when given at 6, 10 and 14 weeks to South African infants. Our results revealed that this vaccine is safe and immunogenic in black South African infants with an overall anti-HBs seroprotective rate of 93.0% based on a titre of ⩾ 10 mIU/ml. During manufacture of Hepaccine B, no denaturing agents are used, pre-S 1 and pre-S 2 antigen components are thus preserved and a heat treatment step increases the immunogenicity of the vaccine and inactivates any residual activity. Our study confirms the good immunogenic properties of Hepaccine B at this relatively low dose (1.5 µg) which has been reported in several independent studies in Indonesia, Korea and the Philippines.[9-11] The post-vaccination blood samples in this study were taken 3 months after the last inoculation at 27 weeks. In the absence of pre-immunisation blood levels in this study it is unlikely that high levels of maternal antibody could be skewing our results. A previous study conducted in 1989 by Manyike and colleagues[12] showed that the overall HBV exposure rate for the Ga-Rankuwa population (situated close to Soshanguve) was 28.9%. Although no data were collected for the 0 - 4-year age group, only 6% of children had evidence of total HBV exposure in the 5 - 9-year age group, 9.9% in the 10 - 15-year age group and 28.6% in the 20 - 24-year age group. From the low level of HBV seropositivity and the absence of anti-HBs carriers in young children in this population, it is unlikely that the 93% of protective antibodies present in the infants could have represented a boosting effect in infants already exposed to the virus. Furthermore we now have evidence from recent work indicating a 96% seroprotective rate of Hepaccine B at 9 months after babies have received the 3 doses at 6, 10 and 14 weeks. The good immunogenic properties of Hepaccine B in this study and in other studies elsewhere in the world contrasts with the only report by Milne and colleagues,[6] who conducted field evaluations of newborns in Vanuatu and the Solomon Islands, where high failure rates were observed even when larger doses of this vaccine were used. Race or genetic factors could have accounted for the difference in the results obtained from the different studies. However, the decrease in anti-HBs levels in the South African infants will continue to be monitored, as will the occurrence of breakthrough infections.

The schedule of Hepaccine B is short: 0, 1, and 2 months. This schedule has great benefit in reducing drop-outs and, most importantly, the infants get their full protection earlier. Although this study only evaluated seroconversion and geometric mean titres 3 months after the third inoculation and not after doses 1 and 2, the field trial conducted in Indonesia showed that 97.41% of infants seroconverted after the first inoculation, 98.03% after the second inoculation and 99.09% 3 months after the third inoculation with geometric mean titres being 75.86, 114.81 and 128.82 mIU/ml, respectively.[9] Currently the populations of many developing countries with high rates of hepatitis B infection do not benefit from hepatitis B vaccination, because of misperceptions that plasma-derived hepatitis B vaccine may be infectious and also that donors are not able to finance expensive recombinant vaccine. The use of an affordable hepatitis B vaccine, such as has been implemented in the South African Expanded Programme on Immunisation and elsewhere, would greatly facilitate the prevention of hepatitis B in developing countries.

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