Clinical trial to evaluate immunogenicity and safety of inactivated hepatitis A vaccination starting at 2-month-old children

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Active immunization with hepatitis A vaccine has been shown to provide long-term protection against hepatitis A virus (HAV) infection. However, few data are available regarding use of the hepatitis A vaccine in children under two years of age. The present study was conducted to test the safety and immunogenicity of inactivated hepatitis A vaccine administered to infants, and to evaluate the correlation between mother and infant anti-HAV antibodies. A total of sixty healthy children, two months of age, were enrolled in this study and immunized with 360 EU of inactivated hepatitis A vaccine (Havrix) according to the two, four and six months of age schedule. Blood sampling was performed prior to the first vaccination and one month after the third vaccination at seven months. Venipuncture was also done on mother on admission. The reactogenicity was expressed as the percentage of reported local and systemic reactions. The most common side effects were erythema on the injection site and fever. Infants with passively transferred maternal anti-HAV antibodies had a reduced anti-HAV GMT after vaccination. On admission, only one infant and his mother were seronegative and seroconversion was only detected in this infant. One month after the third dose seven infants (12.3%) were found to be seronegative. The infant without passively acquired maternal anti-HAV had the protective levels with a GMT of 3176 mIU/ml one month following the third dose. There was a significant positive correlation between the titers of mother and infant anti-HAV antibodies ($n = 0.96$, $p < 0.001$) on admission. Hepatitis A vaccine showed no immunogenicity in infants with presence of maternal antibodies. Hepatitis A vaccine is safe but it should be used after the disappearance of maternal antibodies.

Key words: hepatitis A, vaccine, immunogenicity, side effects, infant.

Until recently hygienic measures and passive immunization with immune globulin were used for preventing hepatitis A. However, these methods provide short-term protection, and infection was delayed to a period when morbidity and mortality of the disease are high. Active immunization with hepatitis A vaccine was shown to provide long-term protection against hepatitis A virus (HAV) infection[1]. The similarities between the epidemiology of hepatitis A and poliomyelitis suggest that widespread vaccination of an appropriate susceptible population can substantially lower disease incidence, eliminate virus transmission, and ultimately, eradicate infection. However, few data are available regarding the use of hepatitis A vaccine in children under two yers of age[2-4]. The present study was conducted to test the safety and immunogenicity of inactivated hepatitis A vaccine administered to infants in the second month of age, and to evaluate the correlation between mother and infant anti-HAV antibodies.

Material and Methods

The participants were recruited from infants seen at Hacettepe University İhsan Doğramacı Children's Hospital Well Baby Clinic from December 1996 to July 1997. Children between eight and 10 weeks of age, born after > 37 weeks of pregnancy with a birth weight greater than

2500 g and afebrile on the day of vaccination were included in the study. Infants with an acute or chronic illness or congenital abnormalities were excluded from the study. Informed written consent was obtained from the parents.

A total of sixty healthy children, two months of age (63 ± 5 days, 59-80 days) were enrolled in this study and immunized with 360 ELISA units (EU) of vaccine (Havrix, SmithKline Beecham Biologicals, Rixensart, Belgium, Lot: VHA185A2) according to a two, four and six months of age schedule. All vaccines were administered intramuscularly into the left deltoid muscle. In associated injections, DPT vaccine was injected on the right-hand side.

Vaccinees were monitored for immediate, early and late side effects. For the first 30 minutes after vaccination every child was observed for signs of anaphylaxis, wheezing and urticaria. For early side effects any local reaction (pain, redness and induration at the injection site), the rectal temperature, and any systemic reaction (drowsiness, loss of appetite, vomiting, diarrhea, and any other adverse events) were recorded by the parents on a diary card for seven days following each injection. Additionally, they were asked to record any adverse events and intercurrent illness requiring medical contact occurring between vaccination days. The reactogenicity was expressed as the percentage of reported local and systemic reactions. One infant did not receive the second injection and the mothers of two infants did not allow drawing of second blood samples. Pre- and post-vaccination blood samples were available for 57 infants.

Two blood samples were taken from the infant and one form the mother. Blood sampling was performed prior to the first vaccination and one month after the third vaccination at seven months of age. All samples were screened for anti-HAV antibodies using Enzymun-Test® Anti-HAV (Boehringer Mannheim Immunodiagnostics, Cat no: 354639). An antibody concentration of > 33 mIU/ml was considered protective. Statistical analysis was done using SPSS.

Results

On admission 58 mothers (98.3%) were found to be seropositive and one infant and his mother were seronegative. The infant without passively acquired maternal anti-HAV had the protective levels with a GMT of 3176 mIU/ml one month following the third dose. Seroconversion was detected only in this infant. Other infants with passively transferred maternal anti-HAV had a reduced anti-HAV GMT after vaccination (Table I). One month after the third dose seven infants (12.3%) were found to be seronegative.

Tablo I. Immunogenicity of 3-dose Inactivated Hepatitis A Vaccine in Infants

	No. of subjects	GMT, (range)*	No. of subjects with anti-HAV positive
Mother	59**	8649 (< 33-114,608)	58 (98.3)
Infants			
Prevaccination	60	2110 (< 33-25,543)	59 (98.3)
One month after the third vaccine	57	263 (50-3,176)	50 (87.7)

* mIU/ml.
** Since two infants were twins, there were 59 mothers for 60 infants.

There was a significant positive correlation between the titers of mother and infant anti-HAV antibodies ($r = 0.96$, $p < 0.001$) on admission. The regression line between HAV antibodies of mothers and two-month-old infants is given in Fig 1.

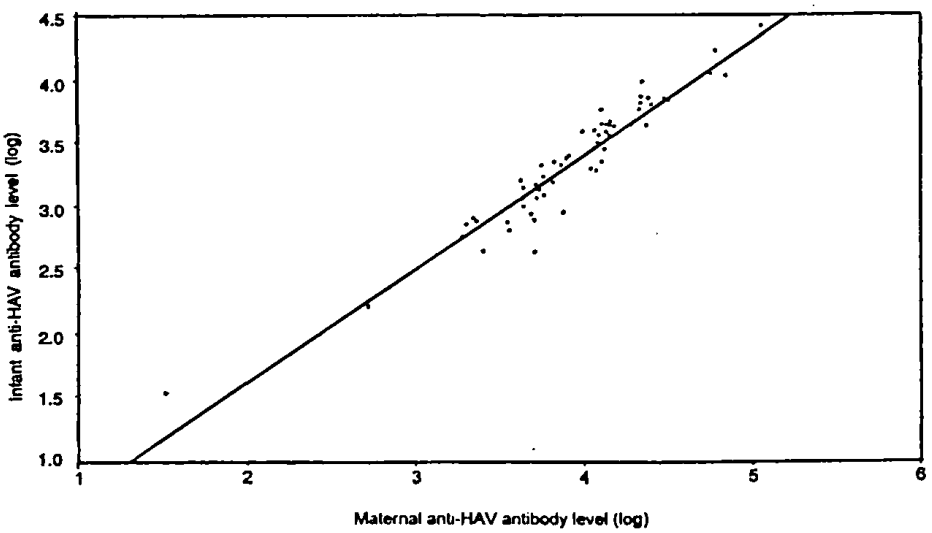

Fig. 1. The regression line between prevaccination levels of anti-HAV GMT levels in infants and anti-HAV GMT levels in their mothers (logarithmic scale) (r2 = 0.91, regression equation: y = 0.89x-0.17).

The most common side effects were erythema on the injection site (up to 6.7%) and fever (Table II). No serious adverse event was seen.

Table II. Number (%) of Infants with Local and General Side Effects within Seven Days After Vaccination

	Vaccination dose no		
	1	2	3
No of subjects	60	59	59
Local side effects			
Pain	–	2 (3.4)	1 (1.7)
Induration	–	3 (5.1)	1 (1.7)
Erythema	4 (6.7)	2 (3.4)	1 (1.7)
General side effects			
Fever > 38.3 °C	2 (3.3)	2 (3.4)	2 (3.4)
Anorexia	–	–	2 (3.4)
Gastrointestinal symptoms (diarrhea, vomiting)	–	–	2 (3.4)
Subjects without side effects	55 (91.7)	54 (91.5)	56 (94.9)

Discussion

Changes in the epidemiology of HAV are evidenced by an increasing age of infection[5-6]. This shift in age of infection to older groups will increase the proportion of cases that cause clinical disease and may increase the case-fatality rate[1,6]. The case fatality rate among persons of all ages is approximately 0.3 percent. However, the case fatality rate is minimal in children aged 5-14 years (0.04%) and considerably higher in adults > 49 years old (2.7%)[1,7]. Although children are less likely than adults to be symptomatic with HAV infection, many children with unrecognized, asymptomatic infection can be a source of infection for others[1,8]. This makes it difficult or impossible to use active or passive immunoprophylaxis on a selective basis[1]. In addition, the availability of hepatitis A vaccine provides an opportunity to substantially lower disease incidence and eradicate infection because humans are the only natural reservoir of the virus[9-11]. As the severity of illness rises with age it is important to administer the vaccine to children and confer durable protection in order to avoid creating a pool of susceptible older subjects[1,5-7].

Few data are available regarding the use of hepatitis A vaccine in children under two years of age[2-4]. Piazza et al.[2] showed that infants vaccinated at five and 11 months of age (720 EU/dose) had 100 percent seroconversion rate. Results from another study indicated that among infants without passively acquired maternal anti-HAV who had been administered hepatitis A vaccine (360 EU/dose) at two, four and six months of age, 100 percent had protective antibody levels with GMT of 794 mIU/mL one month following the third dose[3]. They also reported reduced anti-HAV GMT in infants who had passively acquired antibody because of prior maternal HAV infection[3]. Similarly, in our study infants who were administered Havrix (360 EU/dose) at two, four and six months of age and whose mothers were anti-HAV positive had no response to the vaccination. So optimum immunization age should be determined for each country. Linder et al.[12] reported that protective HAV antibodies were present at birth in 48.3 percent of infants and that by the age of seven months only 13 percent of full-term infants still had protective titers. In our study 98.3 percent of infants by the age of two months had protective titers because of the high rate of maternal HAV seropositivity (98.3%).

In the present study hepatitis A vaccine showed no immunogenicity in infants because of the presence of maternal antibodies at the time of immunization. No severe or persistent side effect was seen among vaccinated children. Hepatitis A vaccine was safe, but it should be used after the disappearance of maternal antibodies. These patients should be followed up to a stage where passive immunity has been eliminated. At this point, a booster vaccination and the child's response to it will help us to evaluate the requirement of the number of vaccinations. This will pose a new model of mass immunization.

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