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Immunogenicity, safety and tolerability of varying doses and regimens of inactivated hepatitis A virus vaccine in Navajo children

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The Navajo are known to be at high risk for hepatitis A virus (HAV) infection. This study investigated the safety and immunogenicity of an investigational, alum-adjuvanted, formalin-inactivated HAV vaccine (VAQTA®) developed by Merck Research Laboratories in Navajo children. One hundred two of 212 children, ages 4 to 12 years, were HAV-seronegative (<10 mIU/ml by an enhanced sensitivity modification of the HAVAB®; Abbott). Ninety of these children received the HAV vaccine. Study participants were given vaccines containing various viral protein concentrations: Group A (n = 18), 6 units; Group B (n = 36), 13 units; and Group C (n = 36), 25 units HAV protein (1 unit ≈ 1 ng viral protein antigen). Three-dose (0, 8, 24 weeks) and two-dose (0, 24 weeks) regimens were compared in subgroups within B and C. The vaccine was well-tolerated and there were no serious adverse reactions; no vaccinee developed hepatitis A. After 1 dose 82 to 100% of children seroconverted (≥10 mIU/ml, modified HAVAB®; Abbott) and 100% seroconverted after 2 doses. After 1 dose the geometric mean titer for antibody was: Group A, 22 mIU/ml; Group B, 18 mIU/ml; and Group C, 38 mIU/ml. After 3 doses geometric mean titers increased to 10 106 mIU/ml in Group A, 7258 mIU/ml in Group B and 11 856 mIU/ml in Group C. Further field studies are indicated to evaluate its use in high risk populations, such as the Navajo.

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INTRODUCTION

American Indians are known to have a high incidence and prevalence of hepatitis A infection. Seroprevalence data in the Sioux Indians of South Dakota revealed high rates of hepatitis A infection.[1] The seroprevalence of anti-hepatitis A virus (HAV) was 63% in those younger than 20 years of age and 90% in those older than 20 years of age. A seroprevalence study at the Crownpoint Boarding School on the Navajo Indian reservation revealed a rate of anti-HAV in kindergarten children of 37%. It increased to 87% by Grade 8.[2] On the basis of a retrospective review of laboratory records from 1987 to 1989 in Indian Health Service hospitals and clinics on the Navajo Reservation we estimated the incidence of clinical hepatitis A infection to be 417 cases 100 000 in children 5 to 14 years of age (unpublished data). The national incidence rate for 5- to 9-year-olds is 23.4/100 000 and the rate for 10- to 14-year-olds is 16.9/100 000,[3] 18- to 24-fold lower than those in the Navajo population.

Recently two inactivated hepatitis A vaccines have been available for investigation in the United States, one developed by Merck Research Laboratories, West Point, PA, and the other by SmithKline Beecham, Philadelphia, PA. Hepatitis A vaccine was protective.[4]

The study objectives were to investigate the safety and tolerability and the optimal dose and dose interval of the inactivated hepatitis A vaccine in 4- to 12-year-old Navajo children.

METHODS

The study protocol was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions and by the Navajo Area Research and Publications Committee and the Navajo tribe. Navajo children ages 4 to 12 years were recruited into the study at two schools on the Navajo Reservation after obtaining written informed consent from their parents/guardians. Two hundred twelve children who consented to be in the study were screened before

receiving the first vaccination to determine if they were seronegative for hepatitis A (<10 mIU/ml; modified[5] HAVAB®; Abbott) (Table 1). Seronegative Navajo children ages 4 to 12 years were eligible to participate in the study. They were excluded from the study if they had: (1) immunodeficiency or neoplastic disease; (2) history of liver disease or were receiving potentially hepatotoxic medications or substances; (3) documented sensitivity to neomycin or thimerosal; (4) immunoglobulin receipt within 3 months before the first vaccination; (5) any other vaccination within 1 month before and 1 month after the first hepatitis A vaccination; and (6) any sign of early upper respiratory infection, influenza or other common childhood infections. Each child received a preenrollment physical examination. Study participants were given sequentially higher doses of vaccine after determining that each dose level was well-tolerated.

Study design. The viral protein concentrations in the vaccines given were: Group A (n = 18), 6 units; Group B (n = 36), 13 units; and Group C (n = 36), 25 units (1 unit ≈ 1 ng viral protein antigen). All children in Group A received three doses of vaccine, the first dose on the day of enrollment and the second and third doses 8 and 24 weeks later, respectively. Children in Groups B and C were randomized to receive either three doses of the vaccine at the same intervals as Group A or to receive two doses, the first on the day of enrollment and the second 24 weeks later.

All children were visited in school by study personnel for 4 days after the day of vaccination in order to assess and record any adverse reactions. Clinical adverse experiences, such as hospitalizations or serious illnesses, were recorded during the study period. Serum specimens were collected before the first dose of vaccine and 4, 10, 24 and 28 weeks later to determine HAV antibody concentrations. Serology was determined by a modified radioimmunoassay[5] (modified HAVAB®) by comparison with the WHO standard antiserum.[6] Titers of 10 mIU/ml and above are considered positive in this assay. Total white blood cell count, hematocrit, serum creatinine and alanine aminotransferase determinations were done before the first vaccination and 4 and 28 weeks after the day of the first vaccination.

Vaccine. The vaccine used (VAQTA®) was a formalin-inactivated, alum-adjuvanted hepatitis A virus (derived from the CR326 strain at the F' attenuation level) produced by Merck Research Laboratories and described in detail elsewhere.[7] It was supplied in single dose vials, stored at 2–8°C and administered intramuscularly in the deltoid area.

Data analysis. Epi Info® Version 5.01b and SAS were used for all statistical computations. Because several observations were censored by detection limits, geometric mean titers (GMT) were calculated by performing censored lognormal regression analyses via SAS PROC LIFEREG.

RESULTS

There were a total of 102 seronegative children of whom 90 (33 female, 57 male) were enrolled. All but 5 who moved out of the area were followed until the final blood drawing 28 weeks postvaccination. Forty-one children were enrolled from School A and 49 children from School B. Seventy-nine (64%) of 123 children were seropositive in School A compared with 31 (35%) of 89 children at School B (Table 1).

Among the 229 vaccinations administered to 90 children, the only side effects observed were slight injection site pain after 4 vaccinations (1.7%), tenderness after 3 vaccinations (1.3%) and mild swelling after 2 vaccinations (0.9%). Two children reported stomach pain after the first vaccination. There was no elevation in alanine aminotransferase.

A high proportion of children (82 to 100%) seroconverted (≥10 mIU/ml; modified HAVAB®; Abbott) after one dose of the vaccine. All children seroconverted after two doses (Table 2).

Separate analyses were performed for antibody responses 4 weeks after the first injection and 4 weeks after the last. Following the first injection, the lower two dose groups had similar antibody responses: GMT 22.5 mIU/ml (95% confidence intervals (CI), 14.7, 34.3) for Group A (6 units); and GMT 18.4 mIU/ml (95% CI, 15.1, 22.3) for Group B (13 units). Group C

TABLE 1. Seroprevalence: percent positive for HAV*

Age (Years)	School A			School B			Total		
	% positive	No. HAV-positive	No. screened	% positive	No. HAV-positive	No. screened	% positive	No. HAV-positive	No. screened
4–6	66.7	34	51	27.3	9	33	51.2	43	84
7–8	78.9	30	38	32.1	9	28	59.1	39	66
9–10	44.4	12	27	36.8	7	19	41.3	19	46
11–12	42.9	3	7	66.7	6	9	56.3	9	16
Total	64.2	79	123	34.8	31	89	51.9	110	212

* 10 mIU/ml, modified[5] HAVAB® (Abbott).

TABLE 2. Antibody response at 4, 10, 24 and 28 weeks in children receiving 2 or 3 doses

Dose (Units)	Schedule	Week 4			Week 10			Week 24			Week 28		
		SC*		GMT (mIU/ml)	SC		GMT (mIU/ml)	SC		GMT (mIU/ml)	SC		GMT (mIU/ml)
6	0,8,24	88	(15/17)†	22	100	(18/18)	1491	94	(17/18)	293	100	(18/18)	10160
13	0,8,24	82	(14/17)	19	100	(18/18)	2180	100	(18/18)	588	100	(18/18)	7258
25	0,8,24	100	(17/17)	38	100	(17/17)	3836	100	(16/16)	1908	100	(16/16)	11856
13	0,24	89	(16/18)	18	No dose at week 8			83	(15/18)	18	100	(18/18)	2871
25	0,24	100	(18/18)	39	No dose at week 8			94	(15/16)	47	100	(15/15)	8372

* SC, percent who seroconverted.
† Numbers in parentheses, number of children who seroconverted.

(25 units) had significantly higher antibody response, with a GMT of 38.2 mIU/ml (95% CI, 33.1, 44.1). No significant differences were seen for different age or sex groups.

A regression model was fit that simultaneously estimated the effects of dose and vaccination schedule on antibody titer after the final injection. Schedule and dose were both important factors. Adjusting for dose children who received 3 injections had a geometric mean titer 122% higher than those who received 2 injections ($P < 0.0001$). Adjusting for schedule children who received the 25-unit dose had a geometric mean titer 90% higher than those who received either the 6- or 13-unit doses ($P = 0.0004$).

While the child's sex was not related to vaccine response at the end of the series, age was a significant factor. Adjusting for dose and schedule, children younger than 8 years of age at study entry had antibody responses 81% higher than children 8 and older (95% CI, 32, 148 or $P = 0.0003$).

DISCUSSION

The vaccine was well-tolerated and there were no serious adverse reactions. One injection of the vaccine produced high seroconversion rates with all three concentrations of the vaccine. The highest seroconversion rates after a single dose were obtained with the vaccine containing 25 units of protein (Group C). This is comparable to a report of a GMT of 35 mIU/ml obtained after one 25-unit dose of the same vaccine in healthy 2- to 16-year-old children.[8] Three injections of vaccine produced high GMTs of anti-HAV at all three dosages tested. Although all groups had high rates of seroconversion, the maximal response was seen in the group who received the highest concentration of protein (25 units) and three doses of the vaccine. It is not known whether these high titers of antibodies are required for long term protection of individuals. Further work and long term follow-up will be needed to determine if an increased GMT is associated with longer lasting protection against disease.

The seroprevalence rate for anti-HAV observed in this population is one of the highest reported in the literature. Although hepatitis A is a mild disease, fatal disease can occur. There is also significant associated loss of time from school and work. Although this vaccine was highly protective in a specific clinical trial,[4] further surveillance studies are indicated to provide information on persistence of antibody and protection after exposure.

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