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RAPID COMMUNICATION

Safety and efficacy of hepatitis A vaccine in children with chronic liver disease

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Abstract

AIM: To study the safety and efficacy of hepatitis A vaccine (HAV) in children with chronic liver disease of various etiologies.

METHODS: Eleven children with chronic liver disease and thirteen age- and sex-matched controls negative for HAV antibodies were vaccinated against hepatitis A after they gave their informed consent. Children with uncontrolled coagulopathy or signs of hepatic decompensation were excluded. The vaccine (Havrix: 720 ELISA units in 0.5 mL, from GlaxoSmithKline Biologicals) was given intramuscularly in the deltoid in 2 doses 6 mo apart. Children were tested for HAV antibodies one and six months after the 1st dose and one month after the 2nd dose. Total serum bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were determined immediately before and after one month of the 1st dose of the vaccine.

RESULTS: Only 7 out of the 11 patients were positive for HAV antibodies after the 1st dose of the vaccine, as compared to 100% of the controls. One month after the 2nd dose, all patients tested were positive for HAV antibodies. No deterioration in liver functions of patients was noted after vaccination. No adverse events, immediate or late, were reported by the mothers after each dose of the vaccine.

CONCLUSION: Hepatitis A vaccine is both safe and effective in this small studied group of children with chronic liver disease. Given the high seroconversion rate, post-vaccination testing for HAV antibodies is not needed.

Key words: Children; Chronic liver disease; Hepatitis A; Hepatitis A vaccine

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INTRODUCTION

Hepatitis A virus (HAV) infection is common. In general, hepatitis A is a self-limited illness with a recovery time measured in months[1]. Young children are often asymptomatic, whereas adults are more likely to be symptomatic and may present with jaundice. Although most patients have a relatively quick recovery without long-term sequelae, about 15% may have a prolonged cholestatic syndrome or a relapsing course over 6-9 mo. A smaller subset will progress to fulminant hepatic failure and death or transplantation, with estimated case fatality rates ranging from 0.01%-0.03% to 0.2% of cases among hospitalized patients[2,3]. Two major risk factors have been identified in patients who developed fulminant hepatic failure: age over 40 years and the presence of underlying chronic liver disease (CLD)[2-4].

Apart from the growing evidence that acute hepatitis A has a more severe clinical course and a higher death rate in individuals with chronic hepatitis B[4-6], and that there is an increased risk of fulminant hepatitis A in patients with chronic hepatitis C[7], patients with other chronic liver diseases also appear to be at an increased risk of developing more severe disease[4,5,8,9].

As the pool of patients with CLD grows, and acute viral hepatitis continues to occur with only a slightly reduced incidence, it is inevitable that a greater number of individuals with CLD will be at risk of developing superimposed acute and chronic hepatitis[1]. To minimize the occurrence of acute hepatitis in patients with CLD, a variety of organizations have recommended hepatitis A and B vaccination in these patients[10,11].

Given the growing evidence that hepatitis A super-infection is probably worse in at least some and probably most patients with CLD, vaccination seems reasonable.

In evaluating HAV vaccination in patients with CLD, an effective strategy should include choice of vaccines, in addition to issues related to safety and efficacy of the vaccine[1].

The issue of pre-vaccination screening for hepatitis A in children with chronic liver disease has been discussed in details in a previous report[12]. The aim of the present study was to evaluate the safety and efficacy of hepatitis A vaccine (Havrix, GlaxoSmithKline Biologicals) in a group of Egyptian children suffering from CLD of various etiologies.

MATERIALS AND METHODS

Patients

We included 172 children: 101 children having CLD and 71 healthy age- and sex- matched brothers, sisters and contacts of the patients as a control group. Their age ranged between 2 and 18 years, with a mean of 7.8 ± 4 years. Parental consent was obtained for medical examination, venepuncture and vaccination. The etiological diagnoses of the 101 children with CLD included autoimmune hepatitis (14 children, 14%), cholestatic disorders of infancy (16 children, 16%), hepatitis B virus (HBV) infection (4 children, 4%) and hepatitis C virus (HCV) infection (9 children, 9%). The remaining 58 children (57%) had miscellaneous causes for their CLD.

Inclusion criteria of children with CLD were willingness to participate in the study, any CLD regardless of etiology, no previous history of vaccination against hepatitis A, children of both sexes. Exclusion criteria were children with uncontrolled coagulopathy, children with decompensated liver disease (hepatic coma, massive ascites, frequent bleeders from esophageal varices, repeated spontaneous bacterial peritonitis), children with known immunological deficiency, and infants below 2 years of age (those who will not be vaccinated).

All children were tested for anti-HAV antibodies by a competitive enzyme immunoassay (ELISA) using commercially available kits (Dia. Pro. Diagnostic Bioprobes Srl., Milano, Italy).

The test results were calculated by means of a cut-off value determined by the following formula: Cut-off = (NC + PC)/3 (NC: negative control; PC: positive control), and interpreted as a ratio of cut-off value and optical density ($A_{450\ nm}$) of the sample (or Co/S) (Table 1).

Out of the 101 children with CLD, only 15 cases were negative for hepatitis A (15%) and 11 consented to be vaccinated. Among the controls, only 16 were negative for hepatitis A (22.5%) and 13 consented to receive the vaccine. Among the 11 cases, 4 were diagnosed as cholestatic disorder of infancy, 3 as HCV infection, 2 as glycogen storage disease, 1 as HBV infection and 1 as Wilson's disease.

Two doses of the vaccine (Havrix: 720 ELISA units in 0.5 mL, from GlaxoSmithKline Biologicals) given intramuscularly in the deltoid 6 mo apart. The mothers were asked to report any immediate or late reactions after the vaccine was given.

Total serum bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were determined immediately before and one month after the 1st dose of the vaccine. Testing for anti-HAV antibodies was done at 3 occasions: one and six months after the 1st dose of the vaccine and one month after the 2nd dose of the vaccine.

Table 1 Ratio of cut-off value and optical density ($A_{450\ nm}$) of the sample (or Co/S)

Co/S	Interpretation
< 0.9	Negative
0.9-1.1	Equivocal
> 1.1	Positive

Table 2 Rate of seroconversion in patients and controls 1 and 6 mo after 1st dose and 1 mo after 2nd dose of HA vaccine

Time	Patients (n = 11) n (%)	Controls (n = 13) n (%)	P
1 mo after the 1st dose of HA vaccine			
Positive	7 (63.6)	13 (100)	0.07
Equivocal	2 (18.2)	0	
Negative	2 (18.2)	0	
6 mo after the 1st dose of HA vaccine			
Positive	7 (63.6)	13 (100)	0.09
Equivocal	3 (27.3)	0	
Negative	1 (9.1)	0	
1 mo after the 2nd (booster) dose of HA vaccine			
Positive	11 (100)	13 (100)	0.63
Equivocal	0	0	
Negative	0	0	

HA: Hepatitis A.

Statistical analysis

All patients' data were collected, tabulated and processed using SPSS 12.0 for Windows XP. Categorical variables were compared using Fischer's exact test. Continuous data were expressed as mean ± SD, range and median if appropriate. Repeated measures for HAV IgG were followed in the same group using Freidman test. These variables were compared in both cases and controls by analysis of variance of repeated measures using the general linear model. Paired variables before and after the vaccine was given were compared using Wilcoxon-Signed Rank test, while unpaired data were compared by Mann-Whitney U test. In all tests, $P < 0.05$ was considered statistically significant.

RESULTS

Testing for HAV antibodies in children with CLD, revealed that only 7 out of the 11 children with CLD were positive for HAV antibodies while 100% of the controls were positive for HAV antibodies one and six months after the 1st dose of the vaccine (P = 0.07 and 0.09 respectively) (Table 2). However, all the children with CLD were positive for HAV antibodies one month after the second dose (booster).

Table 3 Comparison of the mean value of seroconversion (Co/S) between patients and controls

Time	Patients (n = 11)		Controls (n = 13)	
	Range	Mean ± SD	Range	Mean ± SD
1 mo after the 1st dose of HA vaccine	0.6-1.6	1.1 ± 0.4	1.5-3.6	2.5 ± 0.97
6 mo after the 1st dose of HA vaccine	0.9-4.8	3 ± 1.3	2.3-6.9	4.7 ± 1.8
1 mo after the 2nd (booster) dose of HA vaccine	3.2-5.3	4.6 ± 0.8	4.2-5.7	4.9 ± 0.7
P	[b]P = 0.003		[a]P = 0.02	

[a]P = 0.02 within controls by Friedman test; [b]P = 0.003 within patients by Friedman test.

Table 4 Comparison of liver function tests before and after vaccination

	Before vaccination		After vaccination		P
	Range	Median	Range	Median	
Patients					
Total Serum Bilirubin (mg/L)	4-210	7	3-250	7.5	9.5
ALT (IU/L)	19-163	42	19-136	27.5	0.11
AST (IU/L)	28-299	38	30-288	43	0.07
Controls					
Total Serum Bilirubin (mg/L)	3-6	5	1-6	4	4.8
ALT (IU/L)	9-21	18	10-27	17	0.93
AST (IU/L)	21-39	27	21-57	31	0.01[b]

[b]P < 0.01 *vs* controls before and after vaccination (Wilcoxon Signed Ranks Test). ALT: alanine aminotransferase; AST: aspartate aminotransferase.

According to the interpretation of results in Table 1, a significant rise in HAV antibodies (Co/S) was noted both in the children with CLD and in the controls over the 3 readings (P = 0.003 and 0.02 respectively) (Table 3).

No changes in liver function were noted after vaccination except for an insignificant rise in AST of the children with CLD (P = 0.07) and a significant rise in AST of the controls (P = 0.01), although which was within the normal AST range. No adverse events, immediate or late, were reported by the mothers after each dose of the vaccine (Table 4).

Comparison of the difference in liver functions before and after vaccination revealed a significant decrease in ALT of the children with CLD after vaccination as compared to the controls (Table 5).

Table 5 Comparison of differences in liver functions before and after vaccination between patients and controls (mean ± SD)

	Bilirubin (mg/L)	ALT (IU/L)	AST (IU/L)
Patients	0.8 ± 17	-11.3 ± 26	14.8 ± 23.8
Controls	-0.18 ± 0.9	0.54 ± 7.3	5.1 ± 6.8
P	0.92	0.03[a]	0.58

[a]P < 0.05 *vs* controls before and after vaccination (Mann-Whitney U test). ALT: alanine aminotransferase; AST: aspartate aminotransferase.

DISCUSSION

HAV vaccine is currently recommended for three groups: communities with endemic HAV infection (> 20/100 000), individuals at an increased risk of HAV exposure, and individuals with an increased risk of developing severe disease[11]. Patients with CLD are considered to be at risk of developing severe disease, and also at an increased risk of HAV exposure. Patients with serological evidence of previous hepatitis A are considered to have probable lifelong immunity. As such, the seroprevalence of HAV markers plays a central role in determining a vaccination strategy[1]. To determine the need of our children with CLD for hepatitis A vaccination, pre-vaccination screening for HAV antibodies was carried out and vaccination was planned for those negative for HAV antibodies. Because of the high seroprevalence of HAV antibodies among our patients and controls, it seems cost-effective to pretest those above 5 years of age, while pre-vaccination screening would be cost-ineffective in those below 5 years of age[12]. In general, targeted vaccination strategies have been found to be the most cost-effective[13]. Even at the lowest estimated anti-HAV be seroprevalenced rates, selective or deferred vaccination is the most cost-effective strategy in patients with CLD, if the recommended HAV vaccination schedule is to be used[14]. The prevalence of anti-HAV must decrease to below 12% before universal vaccination becomes a more cost-effective strategy[1].

Among our studied children with CLD and controls, no immediate or late adverse effects after vaccination were noticed by the mothers. Liver functions were assessed immediately before and one month after the 1st dose of the vaccine. No significant changes were noted in the children with CLD apart from a significant decrease in ALT as assessed by comparing the mean difference (Table 5). Patients with CLD can receive HAV vaccination with little worry about the vaccine-related adverse effects. Since 1980s, hepatitis A vaccine has been studied extensively in individuals of all ages, and has been known to be safe[15-18]. No significant adverse events have been found to be associated with the use of hepatitis A vaccine in patients with CLD[19].

Only 7 out of 11 children with CLD were positive for HAV antibodies while 100% of the controls were positive for HAV antibodies one and six months after the 1st dose of the vaccine. However, one month after the booster dose all the children with CLD (100%) were positive for HAV antibodies. A rise in antibody level as calculated by Co/S was noted in both the children with CLD and the controls over the 3 readings. Similar seroconversion rates have been reported in children with chronic hepatitis B and C[20] and other chronic liver diseases[18]. A booster dose could induce seroprotection in all children[20]. Keeffe and co-workers[19] reported that the mean geometric titer of anti-HAV is significantly lower in patients with CLD than in healthy controls. However, seroconversion to an immune state has been found in approximately 95% of patients with CLD and 98% of healthy controls (seronegative patients can achieve anti-HAV titers of ⩾ 30 kIU/L as

previously defined). A smaller trial in Chinese patients also noted that the seroconversion rates are similar in 65 chronic HBV infection patients given HAV vaccine and healthy controls, although the anti-HAV titer is lower in patients with CLD[21]. Seroconversion in all patients after the 1st dose of the vaccine has been reported by Giacchino *et al*[22] in a group of children with a variety of metabolic liver diseases.

Although studies have demonstrated the immu-nogenicity of HAV vaccine in mild and moderate CLD, the efficacy of HAV vaccines in advanced or decompensated liver disease has not been thoroughly investigated. Smallwood *et al*[23] found that seroconversion can be achieved in only 48.6% of patients with end-stage liver disease awaiting liver transplantation following a normal HAV vaccination schedule. Patients with end-stage liver disease with uncontrolled coagulopathy and signs of hepatic decompensation were not included in our study.

In conclusion, hepatitis A vaccine is indicated for patients with CLD who are negative for HAV antibodies, and should be provided as early as possible in the course of CLD, as the immunogenicity is poor in advanced liver disease and after liver transplantation. In view of the high seroconversion rate for patients with mild to moderate disease, post-vaccination testing is not needed. The vaccine is both safe and effective in children with mild to moderate liver disease.

REFERENCES

1 **Reiss G**, Keeffe EB. Review article: hepatitis vaccination in patients with chronic liver disease. *Aliment Pharmacol Ther* 2004; **19**: 715-727
2 **McNeil M**, Hoy JF, Richards MJ, Lehmann NI, Dimitrikakis M, Gust ID, Lucas CR. Aetiology of fatal viral hepatitis in Melbourne. A retrospective study. *Med J Aust* 1984; **141**: 637-640
3 **Willner IR**, Uhl MD, Howard SC, Williams EQ, Riely CA, Waters B. Serious hepatitis A: an analysis of patients hospitalized during an urban epidemic in the United States. *Ann Intern Med* 1998; **128**: 111-114
4 **Keeffe EB**. Is hepatitis A more severe in patients with chronic hepatitis B and other chronic liver diseases? *Am J Gastroenterol* 1995; **90**: 201-205
5 **Hadler SC**. Global impact of hepatitis A virus infection changing patterns. In: Hollinger FB, Lemon SM, Margolis H, ed. Viral Hepatitis and Liver Disease. Baltimore: Lippincott Williams & Wilkins, 1990: 14-20
6 **Yao G**. Clinical spectrum and natural history of viral hepatitis in a 1988 Shanghai epidemic. In: Hollinger FB, Lemon SM, Margolis H, eds. Viral Hepatitis and Liver Disease. Baltimore: Lippincott Williams & Wilkins, 1991: 76-78
7 **Vento S**, Garofano T, Renzini C, Cainelli F, Casali F, Ghironzi G, Ferraro T, Concia E. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998; **338**: 286-290
8 **Akriviadis EA**, Redeker AG. Fulminant hepatitis A in intravenous drug users with chronic liver disease. *Ann Intern Med* 1989; **110**: 838-839
9 **Kyrlagkitsis I**, Cramp ME, Smith H, Portmann B, O'Grady J. Acute hepatitis A virus infection: a review of prognostic factors from 25 years experience in a tertiary referral center. *Hepatogastroenterology* 2002; **49**: 524-528
10 National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 2002--June 10-12, 2002. *Hepatology* 2002; **36**: S3-20
11 **Weinbaum C**, Lyerla R, Margolis HS. Prevention and control of infections with hepatitis viruses in correctional settings. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 2003; **52:** 1-36; quiz CE1-4
12 **El-Karaksy** H, El-Sayed R, El-Raziky M, El-Koofy N, Mansour S. Cost-effectiveness of prescreening versus empirical vaccination for hepatitis A in Egyptian children with chronic liver disease. *East Mediterr Health J* 2008; **14**: 804-809
13 **Jacobs RJ**, Koff RS, Meyerhoff AS. The cost-effectiveness of vaccinating chronic hepatitis C patients against hepatitis A. *Am J Gastroenterol* 2002; **97**: 427-434
14 **Siddiqui F**, Mutchnick M, Kinzie J, Peleman R, Naylor P, Ehrinpreis M. Prevalence of hepatitis A virus and hepatitis B virus immunity in patients with polymerase chain reaction-confirmed hepatitis C: implications for vaccination strategy. *Am J Gastroenterol* 2001; **96**: 858-863
15 **Innis BL**, Snitbhan R, Kunasol P, Laorakpongse T, Poopatanakool W, Kozik CA, Suntayakorn S, Suknuntapong T, Safary A, Tang DB. Protection against hepatitis A by an inactivated vaccine. *JAMA* 1994; **271**: 1328-1334
16 **Clemens R**, Safary A, Hepburn A, Roche C, Stanbury WJ, André FE. Clinical experience with an inactivated hepatitis A vaccine. *J Infect Dis* 1995; **171** Suppl 1: S44-S49
17 **Furesz J**, Scheifele DW, Palkonyay L. Safety and effectiveness of the new inactivated hepatitis A virus vaccine. *CMAJ* 1995; **152**: 343-348
18 **Ferreira CT**, da Silveira TR, Vieira SM, Taniguchi A, Pereira-Lima J. Immunogenicity and safety of hepatitis A vaccine in children with chronic liver disease. *J Pediatr Gastroenterol Nutr* 2003; **37**: 258-261
19 **Keeffe EB**, Iwarson S, McMahon BJ, Lindsay KL, Koff RS, Manns M, Baumgarten R, Wiese M, Fourneau M, Safary A, Clemens R, Krause DS. Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease. *Hepatology* 1998; **27**: 881-886
20 **Majda-Stanislawska E**, Bednarek M, Kuydowicz J. Immunogenicity of inactivated hepatitis A vaccine in children with chronic liver disease. *Pediatr Infect Dis J* 2004; **23**: 571-574
21 **Tsang SW**, Sung JJ. Inactivated hepatitis A vaccine in Chinese patients with chronic hepatitis B infection. *Aliment Pharmacol Ther* 1999; **13**: 1445-1449
22 **Giacchino R**, Timitilli A, Castellano E, Di Rocco M, Fiore P, Soncini R, Romanò L. Hepatitis A vaccine in pediatric patients affected by metabolic liver diseases. *Pediatr Infect Dis J* 2001; **20**: 805-807
23 **Smallwood GA**, Coloura CT, Martinez E, Stieber AC, Heffron TG. Can patients awaiting liver transplantation elicit an immune response to the hepatitis A vaccine? *Transplant Proc* 2002; **34**: 3289-3290

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