Safety and Immunogenicity of Hepatitis A Vaccine in Patients With Chronic Liver Disease

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Acute hepatitis A superimposed on chronic liver disease (CLD) has been associated with severe or fulminant hepatitis. An open, multicenter study was performed to compare the safety and immunogenicity of an inactivated hepatitis A vaccine in patients with CLD with that in healthy subjects. A secondary objective was to compare the safety of the hepatitis A vaccine with that of a commercial hepatitis B vaccine in subjects with chronic hepatitis C. A total of 475 subjects over the age of 18 years were enrolled into 1 of 5 groups according to history, serological data, and previous diagnosis. Patients in groups 1 (healthy adults), 2 (chronic hepatitis B), 3 (chronic hepatitis C), and 5 (other CLD not caused by viral hepatitis) were vaccinated with two doses of inactivated hepatitis A vaccine, 6 months apart. Patients in group 4 (chronic hepatitis C) received 3 doses of a recombinant hepatitis B vaccine, according to a 0-, 1-, and 6-month schedule. Local injection-site symptoms were the most common reactions reported following vaccination in all groups (35.5% of all doses), with the hepatitis B vaccine eliciting fewer injection-site symptoms than the hepatitis A vaccine (19.8% compared with 37.5%). Although a higher percentage of healthy subjects (93%) seroconverted after a single dose of the hepatitis A vaccine than did subjects with chronic hepatitis C (73.7%) or CLD of nonviral etiologies (83.1%), more than 94% of all vaccinees were seropositive for anti-HAV after the complete vaccination course. At each time point, a lower geometric mean concentration of anti-HAV was observed for each group of CLD patients compared with the healthy control subjects. In conclusion, hepatitis A vaccine was well tolerated and induced a satisfactory immune response in patients with chronic hepatitis B, chronic hepatitis C, and miscellaneous CLD. (HEPATOLOGY 1998;27:881-886.)

Hepatitis A is a widespread global disease, in part, because the HAV is an ubiquitous virus which is easily transmitted by the fecal-oral route. Infection usually causes overt illness in adults and school-age children but is often asymptomatic in younger children. Although hepatitis A does not result in CLD, a small proportion of patients with hepatitis A experience relapsing hepatitis weeks after apparent recovery from acute hepatitis.[1,2] Fulminant hepatitis A is rare but often results in death.[3,4] Fulminant hepatitis occurs primarily in older individuals and in persons with underlying CLD.[4,5]

In an analysis of hepatitis A epidemiological data reported to the Centers for Disease Control and Prevention during 1983 to 1988, the estimated case fatality rate was 11.7% in patients with an underlying diagnosis of chronic hepatitis B virus infection, based on detection of hepatitis B surface antigen (HBsAg), and 4.6% in patients with pre-existing CLD.[5,6] These rates were 58- and 23-fold higher, respectively, than for patients without liver disease. This analysis also demonstrated that fatalities occurred predominantly in the older population (72.4% of deaths were in patients >49 years). During an epidemic of acute hepatitis A in Shanghai, China, in 1988, which was attributed to the consumption of raw clams and occurred mainly in young adults with a mean age of 28 years, the case-fatality rate in HBsAg carriers was 0.05%,[7] which was 5.6-fold higher than in patients without hepatitis B virus infection.[5] The overall lower case fatality rate observed in this epidemic may be caused by the lower mean age of affected patients than what is described in the Centers for Disease Control and Prevention report. Experience from a Japanese institution combined with a review of the Japanese literature also showed that hepatitis A infection was more likely to be severe in patients with chronic hepatitis B and histological chronic hepatitis or cirrhosis; on the other hand, patients who were "healthy" HBsAg carriers had a clinical course which was similar to patients with acute hepatitis A infection alone.[8] The mean age of patients in this Japanese report was 30.7 ± 16.0 years. In contrast, a number of other case series (some small) indicate no difference in the severity and outcome of hepatitis A in patients aged 7 to 31 years, with and without underlying hepatitis B virus infection.[9-11]

Commercially available inactivated hepatitis A vaccine has been extensively studied in persons of all ages and has been shown to be safe and efficacious in preventing both clinical

Abbreviations: CLD, chronic liver disease; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; GMC, geometric mean concentration.

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TABLE 1. Subject Characteristics at Enrollment

	Healthy (n = 188)	Chronic Hepatitis C Vaccinated With Hepatitis A Vaccine (n = 104)	Chronic Hepatitis C Vaccinated With Hepatitis B Vaccine (n = 67)	Chronic Hepatitis B (n = 46)	Other CLD (n = 70)
Mean age (range) (yr)	39.8 (19-73)	40.9 (23-69)†	45.0 (25-67)	38.3 (18-67)	43.1 (20-70)
Gender ratio (M/F)*	47.8/52.2	63.8/35.2	68.7/31.3	71.7/28.3	53.6/46.4
Serological status	• seronegative for markers for hepatitis A, B and C	• anti-HCV positive • seronegative for markers for hepatitis A	• anti-HCV positive • seronegative for markers for hepatitis B	• HBsAg positive in two blood samples 6 months apart • seronegative for markers for hepatitis A	• seronegative for markers for hepatitis A, B and C

NOTE. ANOVA of mean ages was not significant for sex ($P = .91$) and interaction sex-group ($P = .67$), but was significant for group ($P = .0015$). Ratio of males to females was significantly different (Fisher's Exact test, $P = .002$).

Abbreviations: hepatitis A viral marker, anti-HAV; hepatitis C viral marker, anti-HCV; hepatitis B viral marker, HBsAg, anti-HBs, anti-HBc, anti-HDV, anti-HBe.

*Gender ratio expressed in percentage (%).

†Age and sex not recorded for one subject.

illness and subclinical infection.[12-16] The 1995 Bulletin of the World Health Organization reported that inactivated hepatitis A vaccine should be considered in persons with CLD caused by viral hepatitis or other etiologies[17]; the recent recommendations of the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention for pre-exposure protection against HAV infection include hepatitis A vaccination of persons who have CLD.[18] Reports of studies in immunodeficient subjects (human immunodeficiency virus-positive patients and hepatitis B virus carriers) have shown that concurrent illness affects the seroconversion rates and antibody concentration elicited by hepatitis A vaccination.[19-22] The vaccine has, however, been shown to be immunogenic for at least 2 years and to be well tolerated in adults and children with hemophilia when administered subcutaneously (to reduce risk of hematoma).[19,21,23] Thus, a study was undertaken to evaluate the safety and immunogenicity of an inactivated hepatitis A vaccine in patients with chronic hepatitis B and C and with CLD of other etiologies compared with a control group of healthy adults. Additionally, the study incorporated a comparison of the safety of the hepatitis A vaccine to that of a commercially available recombinant hepatitis B vaccine, which is known to have a low reactogenicity profile.[24-26]

PATIENTS AND METHODS

Patients

Study Population and Design. This open, prospective, comparative study was conducted at four sites in the United States and at four sites in Europe. All participants gave written, informed consent before they were enrolled. The study protocol was approved by the respective ethical review committee of each trial center and was conducted according to the requirements of the provisions of the Declaration of Helsinki, as amended in Hong Kong in 1989, and of the Good Clinical Practice Guidelines in operation at the time of initiation of the study. Subjects at least 18 years (without regard to sex, race, or socioeconomic status) were eligible for enrollment in 1 of 5 groups according to history, physical examination, serological data, and previous diagnosis as follows: group 1, healthy adults with serum alanine aminotransferase level $\leq$1.5 times the upper limit of normal and seronegative for markers for hepatitis A, B, and C; group 2, subjects with chronic hepatitis B; groups 3 and 4, subjects with chronic hepatitis C; and group 5, subjects with other moderate CLD that was not caused by viral hepatitis. Table 1 summarizes the serological inclusion criteria with respect to each group. The confirmation of CLD required documentation of previous liver biopsy consistent with the diagnosis or serum alanine aminotransferase level above the upper limit of normal on 2 specimens, at least 6 months apart, that were accompanied by the presence of viral markers indicative of chronic viral infection, i.e., for chronic hepatitis B, this required the presence of HBsAg in two blood samples 6 months apart, and for chronic hepatitis C, the presence of antibody to the hepatitis C virus detected by second-generation assay (EIA-2, Ortho). Subjects with chronic hepatitis C were randomized into 1 of 2 groups to compare the safety of the inactivated hepatitis A vaccine to that of a commercial hepatitis B vaccine. CLD of etiology other than chronic hepatitis B or C included autoimmune hepatitis, alcoholic cirrhosis, biopsy proven chronic hepatitis or cirrhosis, or a biopsy compatible with a diagnosis of primary sclerosing cholangitis, primary biliary cirrhosis, or hemochromatosis. Although many of these chronically ill subjects were expected to be on various medications, patients who had received immunosuppressive therapy or other immune-modifying drugs within 6 months of entry into the study or treatment with interferon within 3 months were excluded. Volunteers with a history of liver transplantation, who were expected to have a transplant within 6 months, or who had history of bleeding esophageal varices, ascites, or hepatic encephalopathy within the previous 3 months were not included. Other exclusion criteria included the following: serum albumin level $<$3.0 g/dL and/or prothrombin time 3 seconds above control or less than 70% (control:patient); anti-human immunodeficiency virus 1 seropositivity or currently diagnosed malignancy.

Materials

The vaccines used in this study, Havrix®, a hepatitis A vaccine containing 1440 ELISA units (EL.U) of inactivated HM175 hepatitis A virus per 1-mL dose, and Engerix-B®, a recombinant DNA hepatitis B vaccine containing 20 μg of recombinant HBsAg per 1-ml dose, were manufactured by SmithKline Beecham Biologicals (Rixensart, Belgium). Hepatitis A vaccine was administered according to a two-dose schedule composed of a single primary dose followed by a booster vaccination 6 months later. Hepatitis B vaccine was administered according to a three-dose (0,1-,and 6-month) schedule. Both vaccines were administered intramuscularly in the deltoid.

TABLE 2. Adverse Events Related/Possibly Related to Vaccination with Hepatitis A and B Vaccines in Healthy Subjects and Persons With CLD

	Hepatitis A Vaccine				HAV vs. HBV Vaccine Hepatitis C	
	Healthy (n = 371)	Hepatitis B (n = 91)	Hepatitis C (n = 200)	Others* (n = 136)	(n = 200)	(n = 197)
Local symptoms	37.2%	44% (P = .279)	37.5% (P = 1.000)	44.9% (P = .125)	37.5%	19.8% (P = .0001)
General symptoms	11.1%	16.5% (P = .007)	24.5% (P < .0001)	27.9% (P < .0001)	24.5%	19.3% (P = .207)

NOTE. The incidence of local and general symptoms in each of the cohorts of CLD subjects was compared separately with that in healthy subjects by Fisher's Exact test.

Abbreviation: HBV, hepatitis B virus.

*Others = chronic liver disease of etiology other than hepatitis B or C.

Methods

Criteria for Evaluation. All participants were given diary cards on which to record any local or systemic symptoms for 3 days after each inoculation. Any other general or local adverse events either observed by the investigator or reported by the vaccinee over the complete course of the study were recorded. Serum alanine aminotransferase was measured before vaccination and was monitored at months 1, 2, 6, and 7 using standard laboratory techniques. In addition, serum albumin, total bilirubin, prothrombin time, and alkaline phosphatase were measured using commercially available methods before vaccination and one month following the final vaccination. Pre-vaccination blood samples were tested in the investigators' laboratories for the presence of anti-HAV, HBsAg, antibody to hepatitis B surface antigen, antibody to hepatitis B core antigen, antibody to hepatitis B e antigen, antibody to hepatitis D virus, and anti-hepatitis C virus using commercially available assays. Post-vaccination titers of anti-HAV were determined at months 1, 2, 6, and 7 at the University of Miami Hepatology Laboratory using a commercial enzyme-linked immunosorbent assay (Boehringer Enzymun Kit)[27] calibrated by use of World Health Organization international standard reference serum and expressed in mIU/mL. The assay cut-off is set at 33 mIU/mL, which corresponds to the lower quantitation limit of the test; therefore, subjects with titers below 33 mIU/mL were considered seronegative. The geometric mean concentration (GMC) of anti-HAV was calculated by group at all time points at which blood samples were obtained using the log-transformation of titers and by taking the anti-log of the mean of these transformed values. One-half the cut-off value was arbitrarily assigned to negative results. Following the course of vaccination with the recombinant hepatitis B vaccine at month 7, blood samples were drawn for anti-hepatitis B surface antigen titration using a radioimmunoassay test (AUSAB, Abbott Laboratories, Chicago, IL). Subjects with titers <1 mIU/mL, the assay cut-off, were determined to be seronegative; anti-hepatitis B surface antigen titers ≥ 10 mIU/mL were considered to be protective.[28]

Statistical Methods. The study was powered at 80% to detect a 15% difference in seroconversion rates between groups. Fisher's Exact test was used to compare the following: seroconversion rates for anti-HAV in each of the chronically ill groups to that in healthy subjects; the ratio of males to females between groups; the incidence of local and general symptoms in each of the cohorts of chronically ill subjects separately to that in the group of healthy subjects; for the incidence of signs and symptoms following vaccination with hepatitis A vaccine to that induced by hepatitis B vaccine in subjects with chronic hepatitis C. Bonferroni correction was applied for multiple testing in comparison of seroconversion rates. ANOVA was used to compare mean ages between groups and gender and interaction between groups and sex. The analysis of covariance was used to compare titers between groups and the effect of age and center on anti-HAV titers. When significance was detected in GMCs, Dunnett's test was used to compare anti-HAV titers in each of the chronically ill groups to that in healthy subjects. The general linear model was used to analyze the effect of origin or severity of the disease within groups or the duration of disease between groups of chronically ill subjects on GMCs of anti-HAV titers.

RESULTS

Table 1 details the demographic characteristics of the 475 subjects enrolled in the 5 study groups. Seven diagnostic subgroups were represented by the seventy subjects with CLD of etiology other than chronic hepatitis B or C, as follows: 17 subjects with alcoholic cirrhosis; 10 subjects with autoimmune hepatitis; 9 subjects with cirrhosis; 2 subjects with hemochromatosis; 15 subjects with primary biliary cirrhosis; 4 subjects with primary sclerosing cholangitis; and 13 subjects classified by the investigators as CLD other than hepatitis B or C but with unspecified origin.

Safety and Reactogenicity of the Vaccine

A total of 995 diary cards were returned for the 997 doses of vaccine administered (99.8% compliance overall), including 800 doses of hepatitis A vaccine and 197 doses of hepatitis B vaccine. Sixteen patients did not receive a booster dose of hepatitis A vaccine (408 subjects [188 from group 1, 104 from group 2, 46 from group 3, and 70 from group 5] were expected to receive 2 injections, for a total of 816 injections; however, the actual number of injections was 800). Four subjects did not receive their booster dose of hepatitis B vaccine (67 subjects were expected to receive 3 injections, for a total of 201 injections; however, the actual number of injections was 197). The general medical history of several subjects included baseline symptoms such as fatigue, headache, and anorexia. Investigators made the clinical judgment as to whether an event was beyond the usual variation of the chronic health status and should be regarded as an adverse event resulting from vaccination. Table 2 details the incidence of adverse events reported over the 4-day follow-up period after vaccination (day of vaccination plus 3 subsequent days). Symptoms were generally categorized as mild to moderate in severity and all resolved spontaneously. One serious adverse event was reported which was deemed to be vaccine related, i.e., a healthy subject (group 1) having a vasovagal reaction shortly after receiving the first dose of hepatitis A vaccine. The subject recovered after iv hydration and subsequently received the booster dose without further incident. No clinically significant change in serum alanine aminotransferase levels was noted in any vaccinee at any time point over the course of the study. A few mild, asymptomatic, and transient

TABLE 3. Seroconversion Rates and GMT

	Timing	(n)	Seroconversion (n)	Seroconversion %	GMC	95% Confidence Interval
Group1: healthy adults	month 1	185	172	93.0	175	150-206
	month 2	186	162	87.1	100	87-115
	month 6	180	132	73.3	74	63-87
	month 7	167	164	98.2	1315	1086-1593
Group 2: chronic hepatitis B	month 1	43	36	83.7	93	68-127
	month 2	46	33	71.7	69	49-97
	month 6	45	23	51.1	43	31-60
	month 7	44	43	97.7	749	519-1080
Group 3: chronic hepatitis C	month 1	99	73	73.7*	77	60-98
	month 2	97	55	56.7*	47	38-58
	month 6	93	35	37.6*	32	26-40
	month 7	87	82	94.3	467	345-631
Group 5: others	month 1	65	54	83.1*	112	83-149
	month 2	66	48	72.7*	64	50-81
	month 6	63	40	63.5	44	36-53
	month 7	63	60	95.2	562	403-783

NOTE. Month 1, etc.: blood sample obtained one month after dose 1, etc. Seroconversion rates in each group of CLD patients were compared with that in healthy subjects by Fisher's Exact test. For calculation of GMCs, negative values were given an arbitrary value of one half the cut-off. 95% confidence interval = lower and upper 95% confidence interval.

Abbreviations: GMC, geometric mean anti-HAV concentration; others, CLD of etiology other than hepatitis B or C; seroconversion, seropositive for anti-HAV with titer ≥33 mIU/mL.

*$P < .01$.

increases in aminotransferase levels occurred which did not generally correlate with administration of vaccine; none was considered to be vaccine related. A comparison of pre- and post-vaccination serum albumin levels, total bilirubin and prothrombin times did not reveal any marked fluctuation in any subject regardless of health history.

Immunogenicity of the Vaccine

Table 3 details the seropositivity rates and geometric mean anti-HAV concentrations of the total study population. After the first dose of hepatitis A vaccine, a statistically significant higher percentage of healthy adults (93%) had seroconverted compared with subjects with CLD caused by chronic hepatitis C (73.7%) or other etiology (83.1%). Although healthy adults also had a higher seroconversion rate than did subjects with chronic hepatitis B (83.7%), this difference was not statistically significant. At month 7, no significant difference was detected in seroconversion rates between healthy subjects and any of the groups of patients with CLD. For each time point, a lower GMC was observed for each group of patients with CLD in comparison with the control group of healthy subjects ($P = .0001$ in all cases). At each time point, Dunnett's test confirmed statistically significant lower GMC in each group of patients with CLD compared separately with GMC in healthy adults. No influence of study site was shown; however, a significant interaction was detected between the categorical variables of sex and patient group. To identify the influence of age on mean anti-HAV concentrations, males and females were analyzed separately. Females consistently had higher GMCs of anti-HAV than did males. For females, age had no significant effect on GMCs; however, at each blood sampling time point, females with chronic hepatitis C infection and other CLD not caused by viral hepatitis had statistically significantly lower GMCs than did healthy females. For males, both age and patient group exerted significant effect on anti-HAV levels. Healthy males had significantly higher antibody levels than did males with chronic hepatitis C at all time points and also at month 1 when compared with males with chronic hepatitis B. In males, age appeared to be inversely related to the magnitude of antibody response.

When additional comparisons, using the general linear model, were performed to determine the effect of disease status on mean antibody concentration within and between groups of liver disease patients, no evidence of statistical difference was shown ($P > .05$ in all cases). In chronic hepatitis B, GMCs were compared according the hepatitis B e antigen status (positive or negative). Subjects diagnosed with chronic hepatitis C were stratified according to the source of infection: injection drug use, receipt of blood products and 'others', i.e., unknown source of infection, and GMCs in each of these subgroups were compared. Within the group composed of patients with CLD of etiology other than viral, GMCs in subjects with cirrhosis were compared with GMCs in subjects with autoimmune disease, and those with liver disease of 'other' causes, i.e., primary sclerosing cholangitis, hemochromatosis. All participants with CLD who received hepatitis A vaccine were subdivided into three categories and GMCs were compared according to the length of time since the onset of illness, as follows: ≤5 years, 5 years to 10 years, and >10 years. In all of the above analyses, no statistical differences were demonstrated.

At month 7, one month after the third dose of hepatitis B vaccine, all subjects in group 4 (chronic hepatitis C) developed protective levels of anti-hepatitis B surface antigen with a GMC of 1,260 mIU/mL.

DISCUSSION

Inactivated hepatitis A vaccine was safe when administered to these cohorts of patients with CLD, as indicated by the low

incidence of symptoms following vaccination. In addition, the vaccines had no adverse effect on hepatocellular status, as indicated by the stability of serum liver enzyme levels as well as total bilirubin, albumin, and alkaline phosphatase levels and prothrombin times. The incidence of general symptoms, both solicited and unsolicited, however, was significantly lower in healthy subjects than in the groups of CLD patients following administration of the inactivated hepatitis A vaccine. The clinical relevance of this finding is uncertain and could possibly be related to baseline symptoms, such as fatigue experienced by subjects with chronic disease. As the empirical standard, hepatitis B vaccine elicited a lower incidence of local injection site symptoms. Otherwise the reactogenicity profile was similar to that of hepatitis A vaccine in subjects with chronic hepatitis C.

The immunogenicity of hepatitis A vaccines is generally evaluated according to two parameters: the seroconversion rate and geometric mean anti-HAV antibody concentrations. Subjects with chronic hepatitis C (73.7%) or CLD of nonviral cause (83.1%) were less likely to seroconvert than were subjects with chronic hepatitis B (83.7%) or healthy subjects (93%) following the first dose of hepatitis A vaccine. However, hepatitis A vaccine induced a satisfactory immune response in these cohorts of CLD patients as indicated by the fact that more than 94% of subjects were seropositive for anti-HAV after the full course of vaccination, irrespective of health status. Lower GMCs of anti-HAV were observed in subjects with CLD compared with healthy subjects, and this finding could affect the kinetics of decrease of antibody titers in the subjects. Natural infection with hepatitis A virus leads to life-long detectable antibody in most individuals, whereas vaccine-induced antibody levels wane over time. The peak antibody response after the booster vaccination is the primary determinant of the persistence of anti-HAV. In healthy adults, vaccine-induced anti-HAV has been observed to decrease rapidly from 1 month after the booster vaccination until 6 months later, followed by a rather constant decrease over the subsequent 2 years, i.e., approximately 14% per year.[29] The rate of decay of mean anti-HAV levels observed in the 5-month period following the blood sampling obtained one month after the primary dose and the booster vaccination could indicate the ability of these chronically ill subjects to retain antibody compared with healthy individuals. In this study, anti-HAV GMC in healthy adults declined by 57% during this time period compared with 54% in subjects with chronic hepatitis B, 58% in subjects with chronic hepatitis C, and 61% in subjects with CLD not caused by viral hepatitis. Although the rate of decline in GMCs was similar in all groups, vaccinees developing a higher anti-HAV level will obviously retain antibody for a longer period than those with lower levels of antibody. As has been reported in other clinical trials,[30-34] women in this study exhibited a stronger immunological response to hepatitis A vaccine than did men, irrespective of chronic health status. Also, as has been previously reported, levels of anti-HAV declined significantly with increasing age in the male cohort.[35] Although no statistically significant differences were determined in GMCs when subjects with CLD were stratified according to various host factors, such as origin of disease or length of illness, these analyses must be interpreted cautiously because of the lack of statistical power and lack of control on type-I error owing to the low number of subjects in each category.

These results indicate that, although antibody response was lower in magnitude in subjects with CLD, more than 94% of patients with miscellaneous viral and nonviral CLD were seropositive for anti-HAV after the full course of vaccination. Moreover, the kinetics of decreasing antibody titer mirrored that seen in healthy adults in this trial and in previously reported studies. In view of the apparent risks posed by acute HAV infection in patients with CLD, it has been recommended that these individuals should be vaccinated against hepatitis A. It can be concluded from this study that hepatitis A vaccination in patients with CLD induces a satisfactory immune response, but patients should be offered testing to determine antibody response following a full course of vaccination.

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