IMMUNIZING CHILDREN TO PROTECT AGAINST THE INCREASING RISK OF HEPATITIS A IN ADOLESCENTS AND YOUNG ADULTS IN SOUTH KOREA

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Abstract. We evaluated the CR326F strain (VAQTA™) derived hepatitis A vaccine in Korean children and adolescents >2 years of age to consider a future immunization program. In our study, the pediatric two-dose regimen of VAQTA™ was found to be generally well tolerated and resulted in 100% (95% CI 94.8, 100.0) seroconversion after 2 doses. Immunizing children with the HAV vaccine routinely should be considered in South Korea, particularly in areas where recent outbreaks have occurred.

INTRODUCTION

Since hepatitis A is not a reportable disease in South Korea, only a few reports studying the prevalence of hepatitis A infection during the last two decades have been published (Fig 1). A seroepidemiology survey from 1982 to 1997 showed that the age specific seroprevalence of HAV antibody decreased dramatically among all age groups (Kim and Lee, 1982; Lim *et al,* 1992; Lee *et al,* 1998; Sohn *et al,* 2000) (Fig 1). Symptomatic hepatitis A in adults was very rare until 1993, but since 1995, the incidence of clinically overt cases has increased significantly (Choi *et al,* 1997; Lee *et al,* 1998). An increasingly susceptible population among young adults may be an important public health problem in the future, since children have been identified as a significant reservoir of HAV transmission and their immunization should be considered a primary goal in the reduction of the overall incidence of hepatitis A disease (CDC, 1996). We evaluated the immunogenicity and reactogenicity of an inactivated hepatitis A vaccine, VAQTA™, in Korean children and adolescents to obtain local data to support a future immunization policy.

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MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Boards of Yongdong Severance Hospital, Yonsei University College of Medicine and the Central Pharmaceutical Affairs Council, National Drug Committee in the Korean Ministry of Health and Welfare. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Subjects were enrolled in an open non-randomized fashion from August 1999 to April 2000. Informed consent was obtained from a parent or legal guardian. Children were excluded if they tested seropositive for HAV antibodies. Safety was measured by recording the temperature for 5 days post-vaccination using diary cards. All subjects were followed for adverse experiences for 14 days after each vaccination and telephone interviews were conducted to verify data. All serious adverse experiences were recorded and reported immediately to MSD Korea and Merck Research Laboratories, USA.

Vaccine

The vaccine, VAQTA™ (formalin inactivated, Alum-Adjuvanted hepatitis A vaccine) was a commercial lot (W5016) available in Korea and was used before the expiration date of 06/04/01. Each 0.5 ml dose of vaccine contained 25 units of purified viral antigen. After physical examination and anti-HAV screening, seronegative children received the first dose intramuscularly in the deltoid muscle and the booster dose at 24 weeks.

Laboratory studies

Venous blood samples were obtained at the first visit, one week prior to immunization, and again four weeks after the second vaccination. Code-labeled serum aliquots of 1.0 ml flat-bottom Nunc cryovials were stored at -70°C in the Yongdong Severance Hospital and sent for HAV antibody testing by modified HAVAB at Merck Research Laboratories (West Pt, PA USA). The modified HAVAB assay has been previously described (Miller *et al,* 1993). Samples ≥ 10 mIU/ml were considered positive.

Statistical analysis

All immunogenicity analyses and summaries were on a per-protocol basis. All subjects who followed the protocol and had serology within defined day ranges were included. A subject, who was enrolled, but was seropositive by modified HAVAB prior to vaccination was excluded from the immunogenicity analyses. All subjects who were vaccinated at least one time and had safety follow-up were included in the safety analysis. Seroconversion rates at 28 weeks after the first injection (4 weeks after the second injection) were calculated along with the corresponding 95% confidence intervals based on binominal probability and assuming normal distribution. The probability of a rate greater than 93% with a sample size of 79 subjects and an expected response of 95% was 80%. All subjects who had safety follow-up data available were to be entered into the safety and tolerability summaries.

RESULTS

Immunogenicity

A total of 110 subjects, 2 to 16 years of age, were recruited. Eight subjects did not fulfill the eligibility criteria and were excluded. A total of 102 subjects, with a mean age of 6.8 ± 3.5 years, received the first dose of vaccine. The gender distribution was as follows: 54 were males (52.9%) and 48 were females (47.1%) (Table 1). Two subjects were lost to follow-up. A total of 100 subjects received the booster dose. Ten subjects refused blood sampling and monitoring after the booster dose because of inconvenience to them. Ninety subjects completed the study and had serology for analysis. Two subjects tested positive for anti-HAV prior to vaccination by modified HAVAB assay and were excluded from the serology analysis. Excluding the two seropositive subjects, 88 subjects were available for a per protocol analysis.

Table 1
Subject accounting.

Subject data	Number (total 102)
Male (age range)	54 (2-16)
Female (age range)	48 (2-16)
1st injection	102
2nd injection	100
Subjects completed (all subjects with serology)	90
Subjects discontinued	12
Adverse experience	0
Lost to follow-up	2
Subject's withdrawal (refused blood sampling)	10

Seroconversion rates measured by modified HAVAB were 100% at Week 28 according to both per-protocol analysis and all subjects with serology analysis. No significant differences in GMT (Geometric mean titer) and seropositivity rates were detected between genders (Table 2). The Week 28 GMT was 7,991 mIU/ml (95% CI 6,481.1, 9852.7) on a per-protocol analysis. (Table 3). The GMT remained virtually unchanged at 7,906.4 mIU/ml (95% CI 6,437.2%, 9,710.8%) when all subjects with serology were analysed.

Safety and tolerability

No serious side-effects were reported after either of the two injections and there were no reports of elevated temperature (≥ 38.3ºC, oral) or fever. Local reactions, limited to pain (2) and pruritus (1), were experienced by 2.9% (3) of subjects after the second injection (Table 3). All local reactions occurred on the same day after vaccination and were transient. Minor adverse experiences were noted in 14 (13.7%) subjects (Table 4) within the 14 day observation period. After the first injection, systemic experiences, of which fatigue (3), upper respiratory tract infection (2) and gastro-intestinal system disorder (2) were the most common symptom reported in seven subjects (6.9%). After the booster injection, 5 subjects (5%) reported adverse experiences, of which upper respiratory tract infection (3), nausea (1), and fatigue (1) were the most common. Most of these experiences for both injections were mild,

Table 2
Seropositivity rate (SPR) and geometric mean titer (GMT) 28 weeks after dose 1 (4 weeks after dose 2) for vaccinees by gender.

Subjects		SPR (95% CI)	GMT in mU/ml (95% CI))
	All (n=90)	100% (94.9-100.0)	7,906.4 (6,437.2, 9,710.8)
PP	M (n=47)	100% (90.6-100.0)	7,684.0 (5,947.0 - 9,928.3)
	F (n=41)	100% (89.3-100.0)	8,358.3 (5,877.1 - 11,887.0)
	All (n=88)	100% (94.8-100.0)	7,991.1 (6,481.2 - 9,852.7)
AS	M (n=49)	100% (90.9-100.0)	7,547.1 (5,891.0 - 9,668.7)
	F (n=41)	100% (89.3-100.0)	8,358.3 (5,877.1 - 11,887.0)

PP: Per-protocol analysis; AS: all subjects with serology analysis; CI: Confidence interval; M: Male; F: Female; All: all subjects

Table 3
Number (%) of cases with systemic complaints within 14 days after injection.

	After the 1st injection (N=102)	After the 2nd injection (N=100)
General symptoms		
Fatigue	3 (2.9%)	1 (1.1%)
Somnolence	0 (0%)	0 (0%)
Fever	0 (0%)	0 (0%)
Tinnitus and posterior neck pain	1 (1.9%)	0 (0%)
Headache	0 (0%)	0 (0%)
Gastro-intestinal symptoms	1 (0.9%)	1 (1.1%)
Nausea or vomiting		
Diarrhea	1 (0.9%)	0 (0%)
Upper respiratory tract symptoms		
Sore throat	0 (0%)	1 (1.1%)
Cough and sputum	2 (1.9%)	2 (2.2%)
Total	8 (7.8%)	5 (5.5%)

Table 4
Clinical adverse experience summary-Days 0 to 14 post any injection.

Subjects category	Number of subjects (%)
Subjects entered	102
Subjects w/ clinical follow-up	102 (100)
Subjects w/o clinical follow-up	0 (0.0)
Subjects with AEs	14 (13.7)
Subjects w/ vaccine-related AEs	8 (7.8)
Subjects w/ serious AEs	0 (0.0)
Subjects discontinued due to AEs	0 (0.0)
Subjects died	0 (0.0)

AE: Adverse experience

transient, and resolved without treatment. Side-effects possibly related to vaccination were reported in a total of 8 subjects (7.8%), mainly after the first dose. Three of these experiences were localized and related to injection, two with pain and one with pruritus. Five experiences were of general nature and thought to be possibly related to vaccination. After the first injection, nausea and vomiting was reported in one subject (1%), fatigue in 3 subjects (2.9%) of which one also reported asthenia (1%). One subject reported tinnitus and mild headache within hours of the first injection, but symptoms resided spontaneously without treatment by the next day. The next vaccination was uneventful and this episode was thought to be unrelated to vaccination by the investigator. After the booster dose, one subject reported nausea and asthenia (1%).

DISCUSSION

The pattern of hepatitis A epidemiology is changing in Asia, with many countries shifting from hyperendenmicity to low endemicity, especially in recently developed and affluent metropolitan communities, such as Seoul, Hong Kong, and Singapore (Yao *et al*, 1993; Lee *et al*, 1999; Barzaga, 2000; Sohn *et al*, 2000; Wang *et al*, 2001). Rapid improvement of living standards and sanitation due to economic growth was reflected in an equally rapid demise of age specific anti-HAV prevalence (Fig 2), whilst paradoxically, at the same time, the incidence of clinical disease increased.

In the past, hepatitis A did not cause major morbidity in adults, since most people acquired

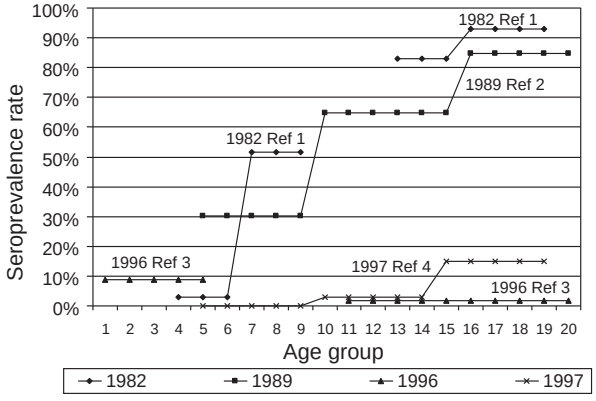

Fig 1–Seroepidemiology survey of hepatitis A in South Korea.

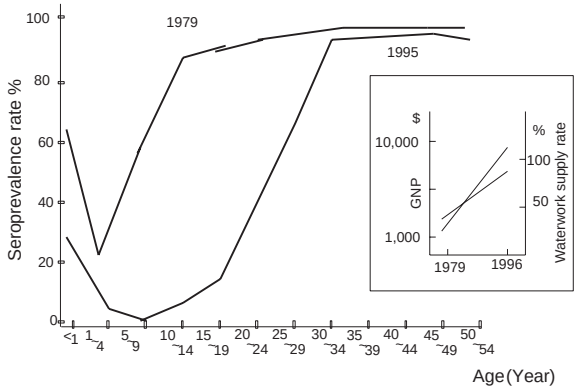

Fig 2–Changing pattern of age specific prevalence of anti-HAV antibody in Korea, 1979 to 1995-1996 (1995-1996 data not shown).

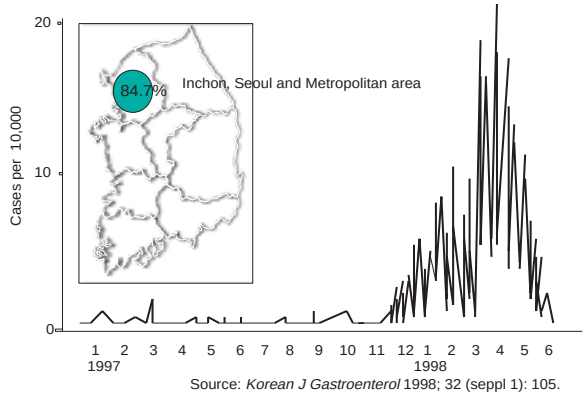

Fig 3–An outbreak of hepatitis A in young adults in South Korea, 1997~1998.

HAV antibodies through infection during childhood, when the disease is mainly asymptomatic. However, reports of clinically overt hepatitis A outbreaks have steadily increased in our adult population since 1995 (Lee *et al*, 1998) (Fig 3). A nationwide survey from January 1997 to June 1998 of suspected hepatitis A cases from 68 general hospitals confirmed 1,519 HAV IgM positive cases (Lee *et al*, 1998). Most of them were young adults and the case-fatality rate was 1.5 per 10^5. The source of infection was often unknown, but might have been related to travel, either for leisure or for business, to endemic areas within Korea or within Southeast Asia, or due to imported food, since there is a national fondness for all types of fresh and raw seafood, and possibly due to migrant workers from endemic regions.

Since 1997, inactivated hepatitis A vaccines have been available in Korea. The hepatitis A vaccine is recommended for use in all persons, including children, who are at increased risk of infection, such as health care professionals, persons attending day care, nurseries or institutions, and travelers to hepatitis A endemic areas.

Inapparent infection in children constitutes a reservoir for the hepatitis A virus. Although immunization with hepatitis A vaccine is currently not recommended in healthy children as a part of the routine immunization schedule in Korea, it needs to be determined if routine immunization of children might be cost-effective from a societal point of view. Epidemiology studies and economic evaluations of hepatitis A vaccination reported elsewhere in various risk groups, such as adolescents in Hong Kong (Lee *et al*, 1999), healthcare workers (Smith *et al*, 1997), frequent travelers (Fenn *et al*, 1998), or military personnel (Buma *et al*, 1998) suggested that vaccination is indeed cost effective. The presence of maternal HAV antibody in Korean infants was observed in 8.3% to 16.7% of infants aged 13 to 16 months, in a recent serological survey (Sohn *et al*, 2002). In Singapore, it was found in 7.7% of infants aged 7-9 months, 0% in 10-12 months and 0.5% in children 1-2 years of age (Chan *et al*, 2001). The optimal age to initiate hepatitis A immunization in Korea is not known at present. Vaccination at 2 years of age should be considered as maternal antibody is known to be undetectable by this age and the vaccine has been shown to be effective for children 2 years of age and above (Werzberger *et al*, 1992).

Three strategic approaches to control hepatitis A in developed countries have been suggested (Das, 1999): strategy I is universal vaccination

of all children, and would be costly, but the most effective. Strategy II is the vaccination of susceptible children only identified after initial screening for HAV antibody. This strategy might be reasonably cost-effective, but neglects the dynamics of transmission from young children to adults, incomplete immunization coverage, willingness to pay if there is no re-imbursement, and less extended marginal benefits, such as herd immunity. Strategy III, where no vaccination is given, would be the most economical option, but of course not effective. Strategy II seems to be more attractive, given our epidemiology, lack of data for a cost-effectiveness analysis, and the present cost of vaccination in Korea. Once local cost-effectiveness data are available, one can advocate for the implementation of strategy I with universal vaccination.

Health authorities implemented national surveillance of hepatitis A in 2001 in South Korea. This will enable us to evaluate more precisely the disease burden of hepatitis A and to conduct cost-effectiveness and cost-benefit studies. It is hoped that the forthcoming results will support the introduction of a routine immunization program.

In conclusion, our study showed that the pediatric two-dose regimen of VAQTA™ was highly immunogenic, generally well tolerated and resulted in 100% seroconversion in Korean children. This would make it a suitable candidate for routine immunization programs.

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