INTRADERMAL HEPATITIS B VIRUS IMMUNIZATION : IMMUNOGENICITY AND REACTOGENICITY

Sayomporn Sirinavin[1], Tikumporn Muchacheap[2], Kalayanee Khupulsup[3], Watcharee Inthraphuwasak[2] and Bencha Petchclai[3]

Departments of [1]Pediatrics, [2]Nursing and [3]Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Abstract. Mass immunization of hepatitis B virus (HBV) vaccine in adults is frequently demanded. However the high cost of conventional immunization is an obstacle to the provision of this vaccine. We investigated the serological response and adverse reactions following administration of a low-dose (1 or 2 μg of yeast-derived HBV vaccine (HB-VAX II, Merck, Sharp and Dohme) intradermally in young adults. Each 1 ml dose of the vaccine contained 10 μg of HBsAg protein. The study population included 58 female volunteers, aged 20-33 years, who were serologically-negative for HBV. They were alternately allocated to 1 μg or 2 μg intradermal dose given by 2 experienced nurses as one or two 0.1 ml injections. Doses were given at 0, 1, and 6 months. Anti-HBs concentration was tested by enzyme-immunoassay on their sera obtained at 1, 6, and 7 months after the first dose. Positive seroconversion (anti-HBs > 10 IU/1) at 7 months was found in 90% (95% CL 79%, 100%) of the 1 μg group and 96% (95% CL 89%, 100%) of the 2 μg group. Local reaction, a transient pigmented macule with an underlying nodule, was found in most volunteers but did not bother them. Intradermal HBV immunization could be an alternative strategy for mass immunization in young adults.

INTRODUCTION

Hepatitis B virus (HBV) infection is an important health problem worldwide. Availability of effective HBV vaccine, since late 1982, makes its control possible. Thailand is considered as a high-endemic country for HBV. More than a half of Thai adults have already been infected and about 5-10% of them are carriers (Solbeslavsky, 1980; Kamolratanakul, 1985). The risk of HBV infection in medical personnel is considered to be non-significantly different from adults in the general population in Thailand (Kamolratanakul, 1985). Therefore, it is not possible to set priorities for HBV immunization for Thai adults according to their occupation. However a large mass HBV immunization in adults is frequently demanded, especially by medical personnel. High cost of conventional intramuscular HBV immunization is an important obstacle in providing mass immunization. Effective, low-cost hepatitis B immunization strategies are needed in order to make this immunization feasible and cost-effective. One way of reducing the cost would be to deliver immunization with a lower dose provided that an adequate antibody response can be achieved. Reports on the successful administration of reduced doses of hepatitis B vaccine intradermally motivated this investigation in Thai medical personnel at Ramathibodi Hospital. In the present study the antibody response and adverse reactions following administration of a low dose (0.1 or 0.2 μg) of yeast-derived HBV vaccine intradermally in young women are assessed.

MATERIALS AND METHODS

Study population

The study population consisted of female volunteers who were nursing students, nurses, and nurse aids, aged 20-33 years at Ramathibodi Hospital, Bangkok. All volunteers were tested for HBV markers (HBsAg, anti-HBs and anti-HBc). Only seronegative individuals were included in the study.

Vaccine and schedule

A yeast-derived HBV vaccine (Merck, Sharp and Dohme, HB-VAX II Lot No. G 4500) was used. Each 1.0 ml dose contains 10 μg of HBsAg protein adsorbed onto approximately 0.25 mg of aluminum hydroxide.

The seronegative volunteers were alternately allocated to a 1 μg or 2 μg dose by their order on the list of names. They were immunized with HBV vaccine by two pediatric nurses who were experienced in intradermal (ID) administration. The 0.1 ml (1 μg) ID injections were administered in the deltoid region with a standard, disposable, 1 ml tuberculin syringe and a 27-gauge needle. A visible cutaneous wheal was regarded as evidence of inoculation. One group was given one ID injection and the other group was given 2 ID injections simultaneously. Doses were given at 0, 1 and 6 months.

Serology tests

Serology tests were performed by enzyme-immunoassay commercial kits : Hepanostika® HBsAg Uni-form (Organon Teknika BV, Boxtel, Holland) for HBsAg, MONALISA® ANTI-HBs (Diagnostics Pasteur, France) for anti-HBs. Passive hemagglutination using in-house reagents (Center for Immunodiagnostic Production, Mahidol University, Bangkok, Thailand) was performed for anti-HBc detection. Tests for these three HBV markers were performed on sera of volunteers before entering the study. Sera were collected from vaccines at 1, 6 and 7 months after the first dose for an anti-HBs test. Anti-HBs concentration more than 10 IU/1 was considered as positive seroconversion.

Assessment of reactogenicity

Each volunteer was asked to fill in a questionnaire about the occurrence of systemic manifestations (fever, arthralgia, myalgia, malaise, rash, headache) and local reactions (erythema, swelling, itching, pain and tenderness, skin discoloration, and subcutaneous nodule formation). The questionnaire was given at the time of injection to be filled out and returned at the time of the next injection or blood drawing.

Statistics

Seroconversion rates were estimated and the corresponding 95% confidence limits were calculated using the normal approximation to binomial. Seroconversion rates were compared between the two groups by means of the chi-square test.

RESULTS

Serological tests of the 95 volunteers by ELISA test revealed positive anti-HBs in 23 (24%), positive HBsAg in 5 (5%) and positive anti-HBc in 3 (3%). Of the 64 seronegative individuals, 6 decided that they could not follow the immunization allocation from the beginning. These resulted in 58 participants with 29 in each groups. The two groups were comparable in their ages and body weights. Means ± SD of ages and body weights of the participants in the 1 μg group vs the 2 μg group were 25.2 ± 4.2 vs 25.2 ± 4.3 years and 48.5 ± 5.5 vs 50.1 ± 7.8 kg respectively.

The anti-HBs serum concentration and seroconversion rates of the vaccines at 1, 6 and 7 months after the first dose are presented in Table 1. A month after the final dose of vaccine (7 months after the initial dose) 90% of the 1 μg group (95% CL 79%, 100%) and 96% of the 2 μg group (95% CL 89%, 100%) had a positive antibody response. The seroconversion rates between the 1 μg and 2 μg group are not statistically significantly different ($p > 0.05$, 95% CL for difference in rates = 7%, 19%).

Side effects of the vaccine, which were found in most volunteers, were limited to the local reactions at the site of administration. A 5-10 mm erythematous macule appeared 24-48 hours after inoculation and resolved over a period of days to weeks. These lesions were not painful, but occasionally pruritic. As the lesions resolved, they tended to leave 1-3 mm pigmented macules which in some instances were associated with an underlying small palpable cutaneous nodule. This local reaction finally disappeared completely. We found that none of our vaccinees had systemic reaction or were unwilling to complete their course because of local reactions and none reported any long-term adverse reactions.

DISCUSSION

Intradermal immunization with low-dose (1-2 μg doses) hepatitis B vaccine was introduced as a

Table 1

Serological response after low dose intradermal hepatitis B immunization.

	1 μg ID × 1 n = 29 (20-33 years)			1 μg ID × 2 n = 29 (20-33 years)		
Anti-HBs (IU/1)	Months after the 1st dose			Months after the 1st dose		
	1 m	6 m	7 m	1 m	6 m	7 m
0	24	18	3 (10%)	22	9	1 (3%)
1-10	3	1	0 (0%)	4	6	0 (0%)
11-20	1	3	2 (7%)	2	4	3 (10%)
21-30	0	4	4 (14%)	0	0	0 (0%)
31-40	0	1	1 (3%)	0	4	1 (3%)
41-50	0	1	2 (7%)	0	2	1 (3%)
> 50	1	1	17 (59%)	1	4	23 (80%)
> 10	2	10	26 (90%)	3	14	28 (96%)

reduced cost alternative to intramuscular vaccination (10-20 μg doses). Investigations on intradermal immunization in healthy adults with various, mostly plasma-derived, vaccines resulted in seroconversion rates ranging from 83-100% (Miller *et al,* 1983; Zoulok *et al,* 1984; Redfield, 1985; Irving *et al,* 1986; Prasetya *et al,* 1986; Goldwater *et al,* 1986; Halsey *et al,* 1986; Fadder *et al,* 1987; Frazer *et al,* 1987; Wahl *et al,* 1987; Lee *et al,* 1987; Heijtink *et al,* 1988). Vaccination schemes involved injections at 0, 1 and 6 months in all investigations. It was suggested from the previous study that differences in sex, age and weight of participants may have contributed to the difference in the results of the studies. Our study was confined to a healthy female population aged 20-33 years old. During our study period, six hospital personnel, aged 36-44 years old, were voluntarily given the HBV vaccine injection by the ID route. One of the two who received 1 μg dose and three of the four who received 2 μg dose had no seroconversion at one month after the third dose, resulting in a seroconversion rate of only 33%. The serological response of the same vaccine given as 0.1 ml dose intradermally by experienced hands was found to be only 61% (95% CL 41%, 81%) in one of our studies of 23 neonates (unpublished data). A study in 30 Gambian neonates also reported a low seroconversion rate of 59% (Whittle *et al,* 1987).

The preparation of HBV vaccine used in this study is alum precipitated, and the ID injection of this kind of preparation is known to cause skin lesions. None of the study participants felt that these reactions were bothersome.

The intradermal route ought to be considered for administration of HBV vaccine for mass immunization in young adults since the dosage can be reduced to 1 : 10 without significantly affecting the seroconversion rate. Correct intradermal deposition of the vaccine is, however, crucial for an adequate immune response (Zuckerman *et al,* 1990). This disadvantage can be overcome in vaccination by experienced hands. The present serology data need to be followed up with information about the effectiveness of this vaccination scheme in HBV protection.

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