THE EVALUATION OF ENGERIX-B IN HEALTHY MALAYSIAN MEDICAL STUDENTS

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ABSTRACT

Fifty medical students were screened for hepatitis B serological markers of whom 42 students entered the study. Those who were found to be negative for all markers were vaccinated with 1.0 ml (20 mcg HBsAg) Engerix-B vaccine intramuscularly in the deltoid region according to the 0, 1, 6 month schedule. Blood samples were taken at 1, 2, 3, 6, 9 months. One month following the first dose, 7% showed detectable AntiHBs with a GMT of 11 IU/l. By the sixth month, just before the third dose was given, 79% seroconverted with a GMT of 2952 IU/l. Three months following the third dose all had seroconverted with a GMT of 18,381 IU/l. No serious adverse reactions were noted and none of the subjects showed evidence of hepatitis B infection during the study. This study thus confirms the high immunogenicity and safety of recombinant yeast-extract hepatitis B vaccine.

Keywords: Hepatitis B, vaccination, yeast-derived hepatitis B vaccine.

SINGAPORE MED J 1990; Vol 31: 314 - 316

INTRODUCTION

Hepatitis B is one of the world's major health problems. There are approximately 285 million or more chronic carriers of hepatitis B worldwide. Of these, 170 million live in South-East Asia and the Western Pacific region.

In Malaysia, the percentage of hepatitis B carrier rate in the general population is 9.4% [1]. Of these, approximately half to three quarters are infected horizontally. Other than the morbidity associated with acute clinical infection, chronic hepatitis B may progress to chronic liver disease which includes chronic persistent and chronic active hepatitis, cirrhosis and hepatocellular carcinoma [2]. Hepatocellular carcinoma is one of the ten most common tumours in the world and there are some evidence that hepatitis B virus is the cause in up to 80% of cases [3]. It has been estimated that hepatitis B carriers face 200 times increased risk of developing hepatocellular carcinoma [4].

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At the present moment, many clinical trials are going on to find a treatment for chronic hepatitis B infection [5]. Until the time comes when there is consistent evidence for an effective treatment of early and late manifestations of hepatitis B infection, control of the disease will have to depend on the use of vaccines.

Hepatitis B vaccine prepared from human plasma has been commercially available since 1982. Despite overwhelming evidence that document its efficiency, widespread acceptance by those who are at the greatest risk of contracting hepatitis B, that is the medical personnel, has been less than expected. This was found to be so since the introduction of hepatitis B vaccination for the staff and students of the Medical Faculty at the National University of Malaysia in 1984.

One of the main fears was that Acquired Immunodeficiency Disease Syndrome (AIDS) might be transmitted to the recipients of this vaccine. Unfortunately, despite numerous studies that eventually refuted this hypothesis [6-9], many are still reluctant to accept this vaccine. The vaccine is also likely to remain expensive because the supply is restricted by the amount of plasma available and by the cost of purifying the hepatitis B surface antigen (HBsAg) to render it free from hepatitis B virus and other possible infectious agents. Thus alternative sources of vaccines that do not depend on human plasma as their source of HBsAg have been developed [10,11]. One of these is the use of recombinant DNA technology to effect synthesis of the surface antigen by a culture of yeast *Saccharomyces cerevisiae*.

This study was undertaken to investigate the efficiency of one of these yeast-derived vaccines which is the Engerix-B vaccine by SmithKline Biologicals. The potential for increased acceptance of this form of hepatitis B vaccine among the staff and students of the Medical Faculty, should be good. The vaccine negates the fear of getting AIDS and with greater demand, the price of hepatitis B vaccine can subsequently be easily affordable.

MATERIAL AND METHODS

Ninety healthy Year III preclinical medical students attending the National University of Malaysia, Kuala Lumpur were recruited on a volunteer basis. Only those who had not received any other hepatitis B vaccine were chosen. Written consent was obtained after providing each participant with information on the source of the hepatitis B vaccine, vaccination and bleeding schedules and the potential risks and benefits of participation in the study.

Fifty subjects were subsequently chosen then screened for the presence of hepatitis B serological markers (HBsAg, AntiHBs, AntiHBc) two weeks prior to the first vaccination. The subjects who were found to be negative for all markers were subsequently vaccinated with 1.0 ml (20mcg HBsAg) of the yeast derived hepatitis B vaccine (Engerix-B Lot ENG 120A4) produced by SmithKline Biologicals. They were all vaccinated intra-muscularly in the deltoid region according to the 0, 1, 6 month vaccination schedule. After each vaccination, local and systemic reactions were recorded for five days on an individual checklist.

Blood samples were obtained at 1, 2, 3, 6, 9 months for serum titres of antiHBs to be measured by enzyme immunoassay using the Ausab antiHBs kit (Abbott Laboratories, North Chicago, Illinois). The antiHBs titres are expressed in IU/l. Blood samples taken at 9 months were also tested for HBsAg and AntiHBc to detect any hepatitis B infection during the study. Seroconversion for hepatitis B is defined as initially AntiHBs negative and subsequently positive for AntiHBs >1 IU/l following vaccination or natural infection.

Table I

Frequency of side-effects following vaccination

Side effects	Engerix - B dose 1 (month 0)	2 (month 1)	3 (month 6)
Pain/local soreness	10/42 (23.8%)	1/42 (2.4%)	0/42 (0%)
Fever (>38.5°C)	5/42 (11.9%)	0/42 (0%)	0/42 (0%)
Malaise	5/42 (11.9%)	0/42 (0%)	0/42 (0%)
Dizziness	1/42 (2.4%)	0/42 (0%)	0/42 (0%)

RESULTS

Of the 50 medical students screened, two were found to be HBsAg and AntiHBc positive but AntiHBs negative. The remaining 48 subjects were negative for HBsAg, AntiHBs and AntiHBc. Unfortunately 6 of the 48 students had to be taken out of the study because they could not be followed-up for the full one year. The subjects were found to be between 21 - 23 years of age with females outnumbering males two to one.As shown in Table I, no severe or serious adverse reactions to the hepatitis B vaccines were noted in any of the subjects. The main side effect was pain or soreness of the injection site lasting between a few hours to one day. Five though developed low grade fever with malaise lasting one day. Most of the complaints were only noted following the first dose of vaccine. Except for one, the rest had no problems with the second and third doses.

Table II

Seroconversion rates (%) and GMTs (IU/L) at indicated times after vaccination: vaccination schedule 0, 1, 6 months*

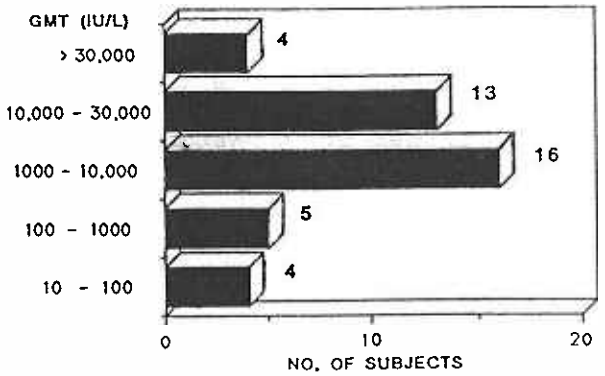
Month	Serconversion rates	GMT (IU/L)
1	3/42 (7%)	11
2	24/42 (57%)	660
3	32/42 (76%)	Not done.
6	33/42 (79%)	2952
9	42/42 (100%)	18381

(* AntiHBs titres done at National University of Malaysia)

Table II shows the seroconversion rates following successive vaccine doses. One month following the first dose, 3 subjects (7%) showed detectable anti-HBs with a geometric mean titre (GMT) of 11 IU/l. Seroconversion to anti-HBs were subsequently detected in 57% at the second month with a GMT of 660 IU/l. Two months after the second dose, 76% of the subjects had seroconverted. By the sixth month, one more subject had detectable anti-HBs bring a total of 79% and a GMT of 2952 IU/l. Three months following the third dose all 42 of the subjects (100%) had seroconverted with a GMT of 18,381 IU/l. Of the 10 subjects who failed to respond after the first two doses, 4 female subjects showed a poor response after the third. At the end of the study none of the subjects showed evidence of hepatitis B infection and they were all tested negative for antiHBc and HBsAg.

Fig 1

AntiHBs titre at 9 months post-vaccination



It should be noted that 4 of the 42 subjects had achieved exceptionally high AntiHBs titre. Although they seroconverted only after the second dose, they obtained titres ranging from 33,000 - 70,000 IU/l (Fig 1) when tested three months after the third dose.

DISCUSSION

This study shows that the SmithKline Biological yeast-derived hepatitis B vaccine (Engerix-B) is well tolerated and highly immunogenic in young healthy Malaysian adults. One hundred percent seroconversion and high AntiHBs levels were achieved after the third dose. This

is comparable with other studies [12-14]. It was also noted that there is no significant difference in the seroconversion rates between the third and sixth month, before giving the third dose (Table II). So, for those at high risk, test for seroconversion can be done two months following the second dose.

Although the minimum protective level is 10 IU/l of AntiHBs, a good response is regarded if the level is greater than 100 IU/l, thereby providing long term immunity. Low responders (levels between 10 - 100 IU/l) generally lack detectable anti-HBs within a few years [15]. From our study, 4 of the subjects were low responders (Fig 1). We thus suggest a fourth dose six months after the third for these subjects with further testing one month following it.

Thus this study confirms that the recombinant yeast hepatitis B vaccine is safe, well tolerated and highly immunogenic. It can be used as an alternative to the plasma-derived hepatitis B vaccine.

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