OVERVIEW

EXPERIENCE OF COMBINED TETRAVALENT DIPHTHERIA, TETANUS, WHOLE-CELL PERTUSSIS AND HEPATITIS B VACCINE IN THAILAND

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Abstract. In 1992, hepatitis B (HB) vaccination of all newborns was officially included in the national expanded program on immunization (EPI), since satisfactory levels of immunity had been attained among the target populations of Chiang Mai and Chon Buri Province during the trial period, 1989 and 1992. In order to facilitate this process and to reduce the administrative costs created by integration of the additional vaccine, the option of combining HB vaccine with the DTP vaccine was investigated. Thus, in 1991 our group performed a clinical study of Smith Kline Beecham Biological's DTP-HB vaccine, administering it to 160 infants of HBsAg negative mothers at the age of 2, 4 and 6 months, respectively. We found the evoked immune responses to be at least equal to, if not higher, than those achieved with the monovalent vaccine. Likewise, any adverse reactions were comparable to those observed after administering either DTP or HB vaccine separately. According to our additional data, we consider HB vaccination at birth, followed by the combined DTP-HB vaccine at the ages of 2, 4, 6 and 18 months, respectively, most advantageous and we would recommend integrating this regimen into the basic immunization service. Thus, the possibility of eradicating hepatitis B infection altogether might eventually be provided.

INTRODUCTION

Hepatitis B virus (HBV) represents a major public health problem in Thailand, where approximately 6 - 10% of the overall population, *ie* 3 to 5 million, have been diagnosed as carriers of HBV (Chainuvati, 1993). A large number of chronic HBV carriers will develop liver diseases, such as chronic hepatitis, cirrhosis, hepatocellular carcinoma (Iwarson, 1985; Tabor, 1985). The one preventive measure offering some promise is the providing of mass vaccinations to all newborns (Chen *et al*, 1996; Tsen *et al*, 1991). Our studies have demonstrated the possibility of preventing perinatal transmission with a success rate of 93-97% by administering HB vaccine to newborns, either separately or in combination with HBIg (Poovorawan *et al*, 1989; 1990; 1992). This vaccine has proven highly efficient in preventing the disease for more than 7 years (Poovorawan *et al*, 1997a). Administration of the second booster by mass vaccination in endemic countries is currently deemed unnecessary.

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HEPATITIS B VACCINATION IN THAILAND

In 1992, the Ministry of Public Health (MOPH) of Thailand included control of hepatitis B infection in its portfolio. To prepare the program, the MOPH in co-operation with PATH (Program for Appropriate Technology in Health), AIDAB (Australian International Development Assistance Bureau), and the Thai Red Cross Society started a demonstration project in two provinces, Chiang Mai and Chon Buri, which concentrated on vaccinating all newborns against HBV during the period of 1989 until 1992. Simultaneously with other EPI vaccines, HB vaccine was given directly at birth, and at the ages of two months and six months, respectively. Under field conditions, HB vaccine could be integrated into the already established basic immunization service. The coverage rate with regard to all three doses of HB vaccine increased from 76.6% in 1989 to 85.2% in 1992. With HB vaccination, satisfactory levels of protective

immunity had been attained among the target population, whereby the carrier rate could be reduced very efficiently (data courtesy of MOPH).

In 1991, MOPH expanded the administration of HB vaccine in order to cover 10 additional provinces, and in April 1992, HB vaccine was officially included in the national EPI, along with the set of vaccines already provided to newborns. Thus, all infants born after 1992 received HB vaccine at birth and at two and six months of age, respectively. There is hope that in the near future the carrier rate among Thai children can be reduced to below 1% and that eventually the disease may be eradicated altogether.

COMBINED TETRAVALENT DIPHTHERIA, TETANUS, PERTUSSIS AND HEPATITIS B VACCINE

However, integrating HB vaccine into EPI also creates some problems due to the increased number of injections which in turn might affect acceptance by the parents. Moreover, the addition of a new vaccine necessitates more physicians and health workers, more available needles and syringes and a higher cold storage capacity, all of which constitute significant issues in developing countries. Therefore, combining HB vaccine with one or more existing EPI vaccines, in particular with the DTP vaccine, is considered an option worth exploring in order to facilitate the process.

In order to select an appropriate formulation for the combined vaccine, which is at least as safe and efficient as each vaccine administered separately, in 1991 our group had performed a clinical study on Smith Kline Beecham Biological's DTPw-HB vaccine, Tritanrix™-HB. The vaccine contained 10 μg of HBsAg, 7.5 Lf diphtheria toxoid, 3.25 Lf tetanus toxoid and 15 OU of whole cell B pertussis per dose. For the study 160 healthy infants born to HBsAg negative mothers were enroled and randomized into thre groups. Two groups (group one and two) received the combined vaccine with different formulations, but containing the same amount of antigens as indicated above. The third group was administered a commercially available DTP vaccine as a control. All vaccinations were performed at 2, 4 and 6 months of age, respectively (Poovorawan *et al*, 1993).

Regarding their reactogenicity, the combined vaccines were comparable to the DTP vaccine in terms of local swelling and general irritability after vaccinations. Among the combined groups, there was a slightly greater frequency of fever reported, but no serious adverse events occurred (Poovorawan *et al*, 1993).

Blood samples were taken at month 2, month 7 (one month after completion of 3 doses), month 18 (before a booster dose), and month 19 (one month after the booster dose) in order to study immunoginicity. We found the combined vaccines elicited protective levels of antibodies against diphtheria, tetanus and pertussis. Similarly, the levels of anti-HBs antibodies were increased and appeared to last for a considerable period of time. These anti-HBs titers were comparable between groups one and two (Poovorawan *et al*, 1993, 1996b).

The seroconversion rate of anti-HBs at month 7 was 98-100% and reached 100% in all vaccinees at month 19. The GMTs at month 7, after complete vaccination with 3 doses, were 211 mIU/ml in group one and 384 mIU/ml in group two. The GMTs at month 19 after a booster dose were 2,971 to 3,854 mIU/ml. We followed these children up to 30 months. In seropositive children (> 10 mIU/ml), the GMTs at 30 months were 206 mIU/ml in group one and 243 mIU/ml in group two. The levels were comparable to those observed in children who were born to HB carrier mothers and received a full vaccination course hepatitis B vaccine (10 Mg of HBsAg) in our long-term studies (Poovorawan *et al*, 1992). The anti-HBs titers were still at the protective level for more than seven years and seemed to be long-lasting without necessitating another booster.

Children who received the combined vaccine had anti-diphtheria titers, measuredwith an ELISA, above the protective level of 0.1 IU/ml at month 7. The respective GMTs were 3.64 IU/ml for group one, 3.61 IU/ml for group two, and in contrast, 3.02 IU/ml for group three (DTPw only). After the booster dose at month 18, the GMTs rose to 6.82 IU/ml and 8.45 IU/ml for groups one and two, respectively. By month 30, they had declined to 0.643 IU/ml and 0.896 IU/ml (Poovorawan *et al*, 1997b).

At month two, *ie* before the first dose, the antibody titers against tetanus among the three groups studied were still high. This could be explained as being due to passive immunity acquired from their

mothers, since in Thailand pregnant women receive 2 doses of tetanus toxoid during the last trimester of pregnancy. In this study, the antibody titer gradually declined until a booster dose was given at month 18 after which it significantly increased, reaching a very high titer one month later. The antibody titers were comparable to those observed in the combined vaccine group and those in the DTP group. The same results were obtained regarding the antibody titers against pertussis which significantly increased in the combined vaccine groups, after the three primary doses and the booster dose had been administered.

In 1994, two years after hepatitis B vaccine had been integrated into the EPI, we initiated another clinical study with the combined DTP-HB vaccine. Our objective was to evaluate two combined diphtheria, tetanus, whole cell pertussis and hepatitis B vaccines containing either 10 μg of hepatitis B surface antigen (HBsAg), *ie* DTPw-HB10 and DTPw-HB5, respectively. A control group received 10 μg of HBsAg (HB10) simultaneously, injected at a different site, with DTPw. All vaccines were given according to the local vaccination schedule at 2, 4 and 6 months of age and all infants had been vaccinated with HB10 at birth. One hundred and twenty-four (124) healthy infants of HBsAg negative mothers were enroled in this open randomized trial in Bangkok, Thailand. Serum antibody titers against vaccine antigens were assessed in blood samples taken prior to the first dose of combined vaccine (at 2 months of age) and one month after the last dose (at 7 months of age) (Poovorawan *et al*, 1996a).

Interim results show that all subjects who received DTPw-HB10 or separate injections of DTPw and HB10 were seroprotected against HBsAg after the 3-dose course (GMT 1,894 mIU/ml and 862 mIU/ml, respectively). Over 90% of the subjects who received 3 doses of DTPw-HB5 were seroprotected against HBs (GMT 356 mIU/ml). All subjects taking part in the study with the exception of one who received DTPw-HB5 had anti-diphtheria antibody titers ≥ 0.1 IU/ml after the complete vaccination course. At this time, all subjects had anti-tetanus antibody titers ≥ 0.1 IU/ml and anti-pertussis antibody titers ≥ 15 EI.U/ml. The safety profile was comparable among the three groups. Based on these results, we would recommend administration of four doses of the DTPw-HB10 combined vaccine given after the initial monovalent HB vaccine,that is, at 2, 4, 6 and 18 months of age (Poovorawan *et al*, 1996a).

From our data it can be concluded that the combined DTPw-HB vaccines can elicit a satisfactory immune response to all four antigens and that their reactogenicity is acceptable. Furthermore, the antibody titers were high and may persist for a long time, as the results of our follow-up until month 48 suggest. Two subsequent studies with the vaccine also showed similar results (Papevangelou *et al*, 1995; Usonis *et al*, 1996).

In 1996, the MOPH launched a pilot project for mass vaccination in Chiang Rai Province, administering the combined DTPw-HB vaccine to 20,000 infants who comprise all the newborns in that province during 1996. Uniformly, all infants received monovalent HB vaccine at birth, followed by a vaccine combining DTPw with HB, at 2, 4 and 6 months of age, respectively. This project has been designed in order to investigate the feasibility, cost-effectiveness, coverage, immunogenicity and vaccine cold-chain, as well as the attitude of the parents towards administering the combined vaccine. This project is still in progress and is planned to be finalized by June, 1997.

THE PROPOSED EPI VACCINE SCHEDULE

The proposed future EPI schedule is as follows:

Month	Vaccine
0	BCG, HB
2	Polio, DTP-HB
4	Polio, DTP-HB
6	Polio, DTP-HB
9-12	Measles or MMR
18	Polio, DTP-HB

In summary, the results of our study on the administration of a combined DTP-HB vaccine to children at birth and at 2, 4 and 6 months of age, respectively, have shown the evoked immune response to be at least as high, if not higher than that attained with the monovalent vaccine. Any adverse reactions were comparable to those observed after administration of either DTP or HB vaccines alone. An additional advantage offered by the combined vaccine is a reduction in costs associated with vaccine administration, as compared to the ones accruing with two monovalent vaccines. Thus, we

would recommend including the combined DTP-HB vaccine into the Thai basic immunization service, which may provide further impetus for the possibility of finally eradicating hepatitis B infection.

ACKNOWLEDGEMENTS

I would like to express my gratitude to the entire staff of the Viral Hepatitis Research Unit, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, for their tireless efforts in this project. I also wish to thank Ministry of Public Health for providing data on mass immunization program in Thailand, Smith Kline Beecham Biologicals, Belgium for their helping us in the researches, Ms Petra Hirsch for reviewing the manuscript.

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