ELSEVIER

Vaccine 17 (1999) 2162–2165

Vaccine

Booster vaccination with recombinant hepatitis B vaccine four years after priming with one single dose

Johan Wiström[a,*], Clas Ahlm[a], Sonia Lundberg[a], Bo Settergren[b], Arne Tärnvik[a]

[a]Department of Infectious Diseases, University Hospital of Umeå, S-901 85 Umeå, Sweden
[b]Department of Infectious Diseases, Danderyd Hospital, S-182 88 Danderyd, Sweden

Received 24 August 1998; received in revised form 3 December 1998; accepted 8 December 1998

Abstract

We here studied the antibody response to a booster dose four years after the administration of one single dose of recombinant HB vaccine. Before receiving the booster dose, levels of protective antibodies (anti-HBs) were generally low and 24/41 (59%) individuals lacked detectable antibodies (< 1 IU/L). Within 14 d of booster vaccination, 36/38 (95%) vaccinees showed levels of antibodies > 100 IU/L. Notably, these levels were at least as high as those of a reference group 12 months after initiation of vaccination according to the standard three-dose vaccination at intervals of 0, 1 and 6 months. In conclusion, one single dose of HB vaccine seemed to confer on young healthy individuals a well preserved B cell memory, disclosed as a rapid and strong antibody response to a second dose four years later. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Hepatitis B; Vaccination; Immunity

1. Introduction

Before plasma-derived hepatitis B surface antigen (HBs) and later recombinant HBs vaccines were introduced on the market, much effort had been paid to optimizing the schedule of vaccination [1]. According to present standard practice, three doses of recombinant vaccine are administered at 0, 1 and 6 months, a regimen by which > 90% of young healthy individuals develop plasma levels of HBs antibodies > 10 IU/L [1,2]. These levels are strongly indicative of protective immunity and moreover, they tend to endure for several years after completed vaccination [3]. Although a highly efficacious regimen is thus established, further work is nonetheless warranted to better understand the vaccine-induced immune response. For example, protection is not necessarily paralleled by the presence of serum antibodies. Several years after vaccination, when antibodies eventually tend to decline, protective immunity may still be quite well preserved [4].

A problem of more immediate practical importance is that a large proportion of hospital staff and other target groups do inadvertently receive only one or two doses of the HB vaccine [5,6] and the immune status of these individuals is unknown. More specifically, it is not known whether the three-dose schedule is indeed important to prime satisfactorily for a later booster vaccination. Of interest, recent data indicate that the administration of two doses of HB vaccine at 0 and 6 months will result in antibody levels similar to those obtained by the standard three-dose schedule [7,8] as well as in retained immunologic memory for HBs antigen 2 years after the initial dose of the vaccine [8].

In 1994, we administered one single dose of recombinant HB vaccine to students entering our medical school. Four years later, they received a booster dose and antibody responses were compared with those of referent subjects vaccinated with three doses according to standard practice.

* Corresponding author. Tel.: −46-90-7852300; fax: +46-90-133006; e-mail: johan.wistrom@infdis.umu.se.

0264-410X/99/$19.00
PII: S0264-410X(99)00012-2

2. Materials and methods

The design of the study was approved by the Research Ethics Committee of the Medical Faculty, University of Umeå, Sweden. Informed consent was obtained from all participating subjects. This was an open, randomized study in which healthy adult volunteers (medical students) were assigned to receive DNA-recombinant HB vaccine (Engerix®, SmithKline Beecham, Brentford, Middlesex, UK) intramuscularly at a dose of 20 μg at 0, 1 and 6 months (group I) or at 0 months followed by a single booster dose 48 months later (group II). Before inclusion in the study, all individuals were shown to be anti-HBs and anti-HBc negative. Serum samples were also obtained from participants of group I at 1, 6, 12 and 48 months and from those of group II at 1, 12 and 48 months after initiation of vaccination as well as 14 d after booster vaccination at 48 months. Ten randomly selected subjects of group II were sampled also on day 1, 3, 5, 7, 9 and 14 d after booster vaccination.

Serum samples were tested for anti-HBs using microparticle enzyme immunoassays (IMx AUSAB® or the AxSYM AUSAB® test kits, Abbott Laboratories, North Chicago, IL). The detection limit was, after calibration, set to ≥1 IU/L. Anti-HBc was analysed using the MEIA AxSYM CORE® test kit (Abbott Laboratories), sensitivity according to the manufacturer <1 PEI unit/mL, (standardized against the Reference Standard of the Paul-Erlich-Institut, Langen, Germany).

In group I, 50 healthy adult volunteers received all three doses of the vaccine. Of these, 42 (19 women, 23 men, mean age 24.3 years, range 20–44 years) subjects were evaluable for serological follow up 12 months after the initial vaccination. In group II, 54 subjects received the primary dose of whom 38 (19 women, 19 men, mean age 24.8 years, range 20–40 years) were available for booster vaccination and serum sampling 48 months later.

3. Results

Twelve months after initiation of vaccination with three doses of HB vaccine (group I), all 42 individuals tested showed anti-HBs levels ≥10 IU/L (Table 1). In 39 subjects (93%), anti-HBs levels were >100 IU/L and in 27 (64%), levels were >1000 IU/L. When subjects receiving one single dose of the vaccine (group II) were tested at 12 months, 31/39 (79%) individuals had nondetectable levels (<1 IU/L) and 8 subjects (21%) had levels between 1–10 IU/L. It should be remarked, however, that a larger proportion of the vaccinees might well have transiently achieved detectable or seroprotective levels of antibodies at 3–6 months, because this is the interval when peak levels have been recorded [8].

At 48 months after initiation of vaccination all participants were still anti-HBc negative. Serum from 30 subjects of group I (13 women and 17 men) available for investigation all had anti-HBs levels >10 IU/L. In 25 persons (83%), levels were >100 IU/L and in 11 (37%) they were >1000 IU/L (Table 1). Among 41 subjects of group II (20 women and 21 men), 24 (59%) lacked detectable antibodies, whereas 14 (34%) had

Table 1
Levels of antibodies to hepatitis B surface antigen (anti-HBs) at various intervals after initiation of intramuscular vaccination with recombinant HB vaccine at 0, 1 and 6 months (group I) or 0 and 48 months (group II)

Levels of Anti-HBs (IU/L)	No. of patients (%)							
	group I				group II			
	1 month (n = 47)	6 months (n = 43)	12 months (n = 42)	48 months (n = 30)	1 month (n = 46)	12 months (n = 39)	48 months	
							Before booster (n = 41)	14 days after booster (n = 38)
<1	26(55)	1(2)			28(61)	31(79)	24(59)	2(5)
1–10	11(23)	1(2)			10(22)	8(21)	14(34)	
11–100	8(17)	11(26)	3(7)	5(17)	8(17)		3(7)	
101–500	2(4)	24(56)	5(12)	7(23)				6(16)
501–1000		4(9)	7(17)	7(23)				7(18)
>1000		2(5)	27(64)	11(37)				23(61)

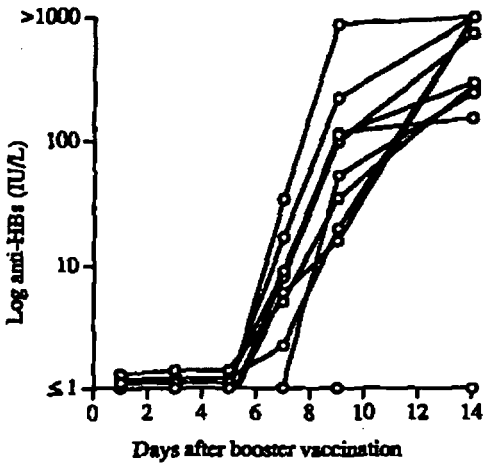

Fig. 1. Kinetics of anti-HBs response to a booster dose of hepatitis B vaccine in 10 individuals vaccinated 48 months previously with one dose of the vaccine. All subjects were tested on day 1, 3, 5, 7, 9 and 14 after the booster vaccination. One individual failed to respond by day 14.

levels 1–10 IU/L and three individuals (7%) had levels 11–30 IU/L.

At 48 months, 38 subjects of group II received a booster dose. 14 d later, 36/38 subjects (95%), had anti-HBs levels >100 IU/L and 23 of them (61%) had levels >1000 IU/L (Table 1). In 10 individuals of group II, the kinetics of the anti-HBs response was studied. From undetectable levels (5 subjects) or levels 1–10 IU/L (5 subjects), 9/10 individuals showed a steep increase of antibodies during the second week after booster vaccination (Fig. 1).

4. Discussion

Four years after priming with one single dose of HB vaccine, a booster dose was found to induce a rapid and strong antibody response. As expected, the antibody response to the first dose was weak or nondetectable. Fourteen days after booster vaccination, however, HBs antibody levels were at least as high as those recorded in reference subjects 12 months after initiation of vaccination with three doses over a 6-month-period.

The present findings might be related to current models to explain how B cell memory is generated. B cell activation through the interaction with antigen may result in differentiation either to an activated effector B cell, ultimately a plasma cell, or to a memory B cell. Plasma cells have a short life span whereas memory cells with somatically mutated antigen receptors are believed to be long-lived [9,10]. In terms of cellular response, the present immunization with one single dose of HB vaccine seemed to result in a poor effector cell response but in an efficient development of memory B cells. Obviously, the stepwise elevation of antibody production aimed at by repeated injections may not be mandatory for the development of a long-term B cell memory. Instead, one single dose seems to prime effectively for a strong and rapid recall antibody response several years later.

The present observations remind of what may be found in subjects several years after vaccination according to standard practice. In spite of declining levels of HBs antibodies, these subjects usually exhibit signs of a well-preserved B cell memory. They respond rapidly to booster vaccination [11–13] and according to in vitro cell analysis, they have a level of immunospecific B cells similar to that of individuals with retained antibody levels [14,15]. Moreover, the decline of HBs antibodies in these individuals is not paralleled by a loss of protective immunity. In a comprehensive survey of the literature, a large number of immunocompetent adults with declining antibody levels have been identified [4]. Among these individuals, no single case of clinical HB virus disease or chronic infection was reported, despite a continuous exposure to HB virus. As discussed by the authors, viral infection may evoke a recall response similar by nature to that evoked by booster vaccination. Since HB virus infection has an incubation period of at least several weeks, the infection might become aborted in due time before lesions appear [4]. If this holds true, the immunologic memory here demonstrated four years after a single vaccine dose might implicate the presence of a significant degree of protection. Direct evidence of such protective immunity is, however, not available. Thus far the conclusion is confined to state that these individuals are well prepared to respond to booster vaccination.

One practical aspect of our results concerns the handling of all those who discontinue HB vaccination after their first dose. Obviously, one additional dose should suffice and this seems valid even when several years have elapsed. In individuals who may be difficult to reach as well as among individuals at low risk, for whom the standard practice may not be considered cost–effective, one dose should indeed be better than none at all. It needs to be emphasized, however, that the present data were confined to healthy individuals and may not be extrapolated to compromized groups. At least, our data indicates that post exposure prophylaxis will be markedly facilitated once a single dose has been previously given.

In conclusion, the injection of one single dose of recombinant HB vaccine induced in young healthy subjects a poor antibody response but an effective long-term B cell memory, disclosed as a capability of evoking a rapid and strong antibody response to booster vaccination four years later.

Acknowledgements

SmithKline Beecham Pharmaceuticals AB, Solna, Sweden, supplied the recombinant hepatitis B vaccine (Engerix®).

References

[1] Hollinger FB. Factors influencing the immune response to hepatitis B vaccine, booster dose guidelines, and vaccine protocol recommendations. Am. J. Med. 1989;87(3A):36S–40S.

[2] Alimonos K, Nafziger AN, Murray J, Bertino JS, Jr. Prediction of response to hepatitis B vaccine in health care workers: whose titres of antibody to hepatitis B surface antigen should be determined after at three-dose series, and what are the implications in terms of cost–effectiveness? Clin. Infect. Dis. 1998;26:566–71.

[3] Centers for Disease Control. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: recommendations of the Immunization Practices Advisory Committee (ACIP). Morb. Mortal. Wkly. Rep. 1991;40(RR-13):11–14.

[4] West DJ, Calandra GB. Vaccine induced immunologic memory for hepatitis B surface antigen: implications for policy on booster vaccination. Vaccine 1996;14:1019–27.

[5] Doebbeling BN, Ferguson KJ, Kohout FJ. Predictors of hepatitis B vaccine acceptance in health care workers. Med. Care 1996;34:58–72.

[6] Smith ER, Banatvala JE, Tilzey AJ. Hepatitis B vaccine uptake among surgeons at a London teaching hospital: how well are we doing? Ann. R. Coll. Surg. Engl. 1996;78:447–9.

[7] Gellin BG, Greenberg RN, Hart RH, Bertino JS, Jr, Stein DH, Deloria MA, Clements-Mann ML. Immunogenicity of two doses of yeast recombinant hepatitis B vaccine in healthy older adults. J. Infect. Dis. 1997;175:1494–7.

[8] Marsano LS, West DJ, Chan I, Hesley TM, Cox J, Hackworth V, Greenberg RN. A two-dose hepatitis B vaccine regimen: proof of priming and memory responses in young adults. Vaccine 1998;16:624–9.

[9] Ho F, Lortan JE, MacLennan IC, Khan M. Distinct short-lived and long-lived antibody-producing cell populations. Eur. J. Immunol. 1986;16:1297–301.

[10] Schittek B, Rajewsky K. Maintenance of B-cell memory by long-lived cells generated from proliferating precursors. Nature 1990;346:749–51.

[11] Horowitz MM, Ershler WB, McKinney WP, Battiola RJ. Duration of immunity after hepatitis B vaccination: efficacy of low-dose booster vaccine. Ann. Intern. Med. 1988;108:185–9.

[12] Jilg W, Schmidt M, Deinhardt F. Four-year experience with a recombinant hepatitis B vaccine. Infection 1989;17:70–6.

[13] Wismans PJ, van Hattum J, Mudde GC, Endeman HJ, Poel J, de Gast GC. Is booster injection with hepatitis B vaccine necessary in healthy responders?A study of the immune response. J. Hepatol. 1989;8:236–40.

[14] Wismans PJ, van Hattum J, de Gast GC, Endeman HJ, Poel J, Stolk B, Maikoe T, Mudde GC. The spot-ELISA: a sensitive in vitro method to study the immune response to hepatitis B surface antigen. Clin. Exp. Immun. 1989;78:75–8.

[15] van Hattum J, Maikoe T, Poel J, de Gast GC. Persistence of immune memory in responders to hepatitis B vaccination who subsequently lost serum anti-HBs. Neth. J. Med. 1991;39:A74.