Rev. Inst. Med. trop. São Paulo
31 *(2): 91-94, março-abril, 1989*

ACTIVE IMMUNIZATION AGAINST HEPATITIS B VIRUS (HBV) WITH LOW-DOSES OF PLASMA-DERIVED VACCINE BY INTRADERMAL ROUTE

Flair José CARRILHO (1), Maria Lúcia QUEIROZ (2), Luiz Caetano da SILVA (1), Luis Edmundo Pinto da FONSECA (1), Celso GRANATO (3), Isabel OBA (3) & Leda OBARA (4)

SUMMARY

Schedule for vaccination against HBV infection has usually been based on three separate injections of 20 mcg of the vaccine by intramuscular route. One of the main shortcomings to its use in large scale programs has been its high cost. Ninety out of 300 health workers were submitted to three injections of 2 mcg of plasma-derived vaccine (PDV) by intradermal (ID) route on days 0, 30, and 180. Anti-HBs was detected in 74 (82.2%) after the second dose and in 80 (88.9%) after the third dose, a non-significant difference. However, levels above 10 times the cut-off were observed in 29 (32.2%) and 77 (85.5%), respectively ($p < 0.001$). The results showed that a low-dose schedule is effective when used in health workers and should be tried with other risk groups.

KEY WORDS: Hepatitis B; Hepatitis B virus; Hepatitis B vaccine; Immunization.

INTRODUCTION

Plasma-derived vaccine is very effective against HBV[1, 3, 4, 8, 15]. The protective antibody against surface antigen (anti-HBs) develops after three doses of the vaccine in more than 90% of the general population[3]. The recomended schedule in most programs of active immunization has been three separate injections of 20 mcg per dose by intramuscular (IM) route in deltoid region[3, 4, 7, 15]. One of the main difficulties to apply this program in underdeveloped countries is its high cost. For this reason different schedules with lower doses have been tried, such as 10, 5 and 2.5 mcg by intramuscular routes[2, 7, 12, 13]. More recently, 2 mcg by intradermal (ID) route was employed, with promising results[5, 8, 9, 10, 13]. However, the samples in most studies were rather small.

The aim of this study was to investigate the efficacy of the plasma-derived vaccine by using 2 mcg by ID route.

MATERIAL AND METHODS

A total of 300 hospital health workers were submitted to a serological study of HBV mar-

(1) Clinical Hepatology Branch, Department of Gastroenterology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil.
(2) Hospital Osvaldo Cruz, São Paulo, SP, Brazil.
(3) Hepatitis Branch, Division of Virology, Instituto Adolfo Lutz, São Paulo, SP, Brazil.
(4) BIESP, Instituto Paulista de Patologia Clínica, São Paulo, SP, Brazil.
Address for correspondence: Dr. Flair José Carrilho, Clinical Hepatology Branch, Department of Gastroenterology, Faculdade de Medicina da Universidade de São Paulo, Av. Dr. Arnaldo, 455, CEP 01246 São Paulo, SP, Brazil.

kers. Hepatitis B surface antigen (HBsAg) and its antibody (anti-HBs) and total core antibody (anti-HBc) were studied by using an enzyme-linked immunoassay (AUSZYME II, AUSAB EIA and CORZYME, respectively, produced by ABBOTT LABORATORIES, U. S. A.). The schedule of active immunization was similar to that used by MILLER et al[11]: one dose at day zero, and subsequent doses at one and six-month intervals using 2 mcg by ID route. Only workers without HBV markers were submitted to vaccination on a voluntary basis.

Seroconversion to anti-HBs was studied immediately before and one month after the third dose. A rough semiquantitative determination was based on the value of the cut-off. It was considered a good antibody response when the value obtained was above then times the cut-off level[8].

In the screening of the 300 workers, anti-HBc was detected in 43 (14.3%), including 9 (3.0%) with HBsAg and 34 (11.3%) of anti-HBs (Figure 1). Only 90 (35.0%) out of 257 workers without HBV markers accepted the vaccination schedule. This group consisted of 68 females and 22 males; with a mean age of 37.4 ± 8.4 years (22 - 56 years).

RESULTS

The results showed that, anti-HBs was detected in 74 (82.2%) and 80 (88.9%) workers, respectively before and after the third dose, a non-significant difference (chi-square = 1.1238, $0.30 > p > 0.20$, Figure 2). However, a good antibody response was obtained in only 29 out of 90 (32.2%) after the second dose and in 77 out of 90 (85.5%) workers after the third dose (chi-square = 50.6909, $p < 0.001$), as shown in Figure 3.

DISCUSSION

Our results clearly show that vaccination with three doses of 2 mcg of HBV plasma-derived by ID route produces a high number of seroconversion to anti-HBs (88.9%). These results agree with those published by MILLER et al[11] and REDFIELD et al[14]. To our knowledge only few papers based on such a schedule of immunization have been published to date[5, 9, 10, 11, 14, 16]. It is worth mentioning that the seroconversion

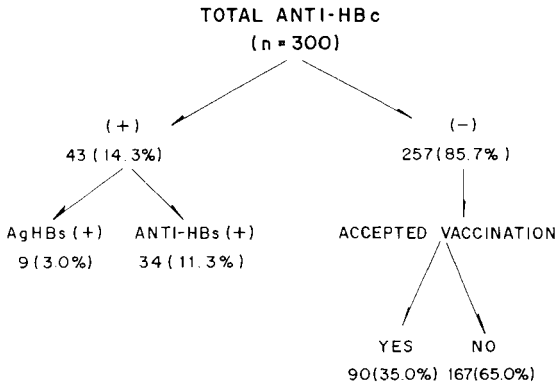

Fig. 1 — Frequency of HBV markers in a screening of 300 hospital health workers.

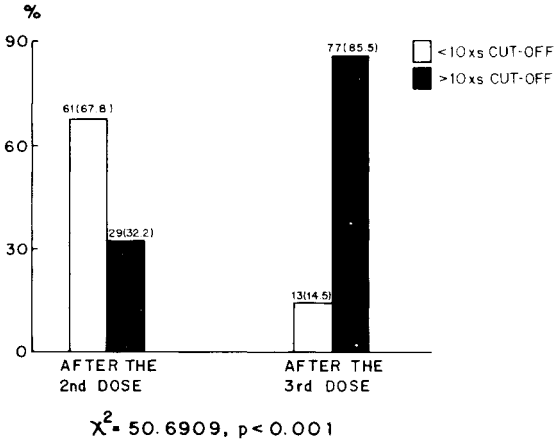

Fig. 2 — Anti-HBS response after the second and third dose of HBV plasma-derived vaccine.

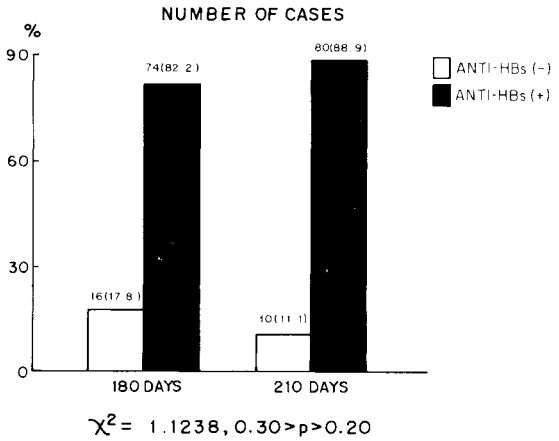

Fig. 3 — Frequency of vaccinated people with good antibody response after the second and third dose.

rate observed in those studies varied from 74.0 to 100.0%. Besides, a comparison between 20 mcg by IM route and 2 mcg by ID route showed no significant difference in the seroconversion rate[5, 14], though the levels of anti-HBs tend to be lower after reduced doses[2, 5, 16].

In our material, a low percentage of subjects (35.0%) accepted to be vaccinated against HBV. The main reason for this high refuse was the unjustifiable fear that plasma-derived vaccine would be contaminated by human immunodeficiency virus[6].

REDFIELD et al[14] and MULLEY et al[12] emphazised that vaccine cost remains a major obstacle for the expansion of HBV vaccination programs.

The low doses schedule used in this study proved to be effective, and, if confirmed in field studies[17], it should be considered in large-scale programs of immunization against HBV.

RESUMO

Imunização ativa contra o vírus da Hepatite B com baixas doses da vacina plasma derivada por via intradérmica.

O esquema habitualmente utilizado para imunização ativa contra o vírus da hepatite B (VHB) consiste em 3 doses de 20 mcg por via intra-muscular (IM) no deltóide. Um dos problemas quanto à sua utilização em larga escala refere-se ao seu custo elevado. Poucas publicações têm se referido a doses menores, de 10 mcg IM ou 2 mcg intradérmica (ID). Pesquisou-se em 300 funcionários da área da saúde o anti-HBc-total. Todos os marcadores foram determinados pela técnica de ELISA. Em 43 (14,3%) o marcador foi positivo, correspondendo a 9 (3,0%) com AgHBs e a 34 (11,3%) com anti-HBs. Aos 257 funcionários sem anti-HBc propôs-se um esquema de vacinação, que foi aceito por 90 (35,0%). Idade média de 37,4 ± 8,4 anos, limites de 22 - 56 anos e 68 do sexo feminino. Esquema: 3 doses de 2 mcg por via ID com intervalos de 1 e 6 meses. O anti-HBs, pesquisado após a 2ª dose mostrou-se positivo em 74 (82,2%) e após a 3ª dose em 80 (88,9%) — diferença não significativa. Contudo, a quantificação do anti-HBs mostrou níveis 10 vezes acima do "cut-off" em 29 (32,2%) e em 77 (85,5%) após a 2ª e 3ª doses, respectivamente ($p < 0,001$). Portanto, o esquema proposto mostrou-se válido para este tipo de população e, apesar da freqüência semelhante de sero-conversão após a 2ª e 3ª doses, há necessidade desta última para aumentar o título de anticorpos.

ACKNOWLEDGMENTS

We are grateful to Doctors JOSÉ DIRCEU PEREIRA, JOSÉ FRUTOS DE OLIVERA, LUCIO OBA, Nurses CATARINA OSAWA and LORE MARX for the technical assistance. The revision of the manuscripts was made by Nurse HANNELORE SPEIERL and Doctors ZILDA PAES DE BARROS MATOS and WILSON MATTOS to whom we are deeply indebted.

REFERENCES

1. ALTER, M. J.; FAVERO, M. S. & MAYNARD, J. E. — Hepatitis B vaccine use in chronic hemodialysis centers in the United States. **J. Amer. med. Ass., 254:** 3200 3202, 1985.

2. DAVIDSON, M. & KRUGMAN, S. — Recombinant yeast hepatitis B vaccine compared with plasma derived vaccine: immunogenicity and effect of a booster dose. **J. Infect., 13** (suppl. A): 31 38, 1986.

3. DIENSTAG, J. L.; WERNER, B. G.; POLK, B. F.; SNYDMAN, D. R.; CRAVENN, D. E.; PLATT, R.; CRUMPACKER, C. S.; OUELLET HELLSTROM, R. & GRADY, G. F. — Hepatitis B vaccine in health care personnel: safety, immunogenicity, and indicators of efficacy. **Ann. intern. Med., 101:** 34-40, 1984.

4. FRANCIS, D. P.; HADLER, S. C.; THOMPSON, S. E.; MAYNARD, J. E.; OSTROW, D. G.; ALTMAN, N.; BRAFF, E. H.; O'MALLEY, P.; HAWKINS, D.; JUDSON, F. N.; PENLEY, K.; NYLUND, T.; CHRISTIE, G.; MEYERS, F.; MOORE, J. N.; GARDNER, A.; DOTO, I. L.; MILLER, J. H.; REYNOLDS, G. H.; MURPHY, B. L.; SCHABLE, C. A.; CLARK, B. T.; CURRAN, J. W. & REDEKER, A. G. — The prevention of hepatitis B with vaccine. Report of the Centers for Disease Control multi center efficacy trial among homosexual men. **Ann. intern. Med., 97:** 362-366, 1982.

5. FRAZER, I. H.; JONES, B.; DIMITRAKAKIS, M. & MAC KAY, I. R. — Intramuscular versus low dose intradermal hepatitis B vaccine. Assessment by humoral and cellular immune response to hepatitis B surface antigen. **Med. J. Aust., 146:** 242-245, 1987.

6. FULTON, J. P.; BODENHEIMER JR., H.C. & KRAMER, P. D. — Acceptance of hepatitis B vaccine among hospital workers: a follow-up. **Amer. J. publ. Hlth., 76:** 1339-1340, 1986.

7. GOUDEAU, A.; DENIS, F.; MOUNIER, M.; DUBOIS, F.; KLEIN, J.; GODEFROY, A.; BALLET, M. & MOUNTIJ, A. — Comparative multicentre study of the immunogenicity of different hepatitis B vaccines in healthy volunteers. **Postgrad. med. J., 63** (suppl. 2): 125-128, 1987.

8. HADLER, S. C.; FRANCIS, D. P.; MAYNARD, J. E.; THOMPSON, S. E.; JUDSON, F. N.; ECHEMBERG, D. F.; OSTROW, D. G.; O'MALLEY, P. M.; PENLEY, K. A.; ALTMAN, N. I.; BRAFF, E.; SHIPMAN, G. F.; COLEMAN, P. J. & MANDEL, E. J. — Long term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. **New Engl. J. Med., 315**: 209 214, 1986.

9. HALSEY, N. A.; REPPERT, E. J.; MARGOLIS, H. S.; FRANCIS, D. P. & FIELDS, H. A. — Intradermal hepatitis B vaccination in an abbreviated schedule. **Vaccine, 4**: 228 232, 1986.

10. IRVING, W. L.; ALDER, M.; KURTZ, J. B. & JUEL JENSEN, B. — Intradermal vaccination against hepatitis B. **Lancet, 2**: 1340, 1986.

11. MILLER, K. D.; GIBBS, R. D.; MULLIGAN, M. M.; NUTMAN, T. B. & FRANCIS, D. P. — Intradermal hepatitis B vaccine: immunogenicity and side-effects in adults. **Lancet, 2**: 1454-1456, 1983.

12. MULLEY, A. G.; SILVERSTEIN, M. D. & DIENSTAG, J. L. — Indications for use of hepatitis B vaccine, based on cost effectiveness analysis. **New Engl. J. Med., 307**: 644-652, 1982.

13. PAPAEVANGELOU, G.; ROUMELIOTOU-KARAYANNIS, A.; VISSOULIS, Ch.; STATHOPOULOU, P.; KOLAITIS, N. & KRUGMAN, S. — Reduction of the dose of hepatitis B vaccine. **J. Infect., 7** (suppl. 1): 69 70, 1983.

14. REDFIELD, R. R.; INNIS, B. L.; SCOTT, R. M.; CANNON, H. G. & BANCROFT, W. H. — Clinical evaluation of low-dose intradermally administered hepatitis B virus vaccine. A cost reduction strategy. **J. Amer. med. Ass., 254**: 3203-3206, 1985.

15. SZMUNESS, W.; STEVENS, C. E.; HARLEY, E. J.; ZANG, E. A.; ALTER, J.; TAYLOR, P. E.; DEVERA, A.; CHEN, G. T. S.; KELLNER, A. & THE DIALYSIS VACCINE TRIAL STUDY GROUP — Hepatitis B vaccine in medical staff of hemodialysis units. Efficacy and subtype cross protection. **New Engl. J. Med., 307**: 1481 1486, 1982.

16. ZOULECK, G.; LORBEER, B.; JILG, W. & DEINHARDT, F. — Antibody responses and skin reactivity after intradermal hepatitis B virus vaccine (letter to editor). **Lancet, 1**: 568, 1984.

17. ZUCKERMAN, A. J. — Appraisal of intradermal immunisation against hepatitis B. **Lancet, 1**: 435-436, 1987.

Recebido para publicação em 14/11/1988.