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Active hepatitis B vaccination of dialysis patients and medical staff

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Active hepatitis B vaccination of dialysis patients and medical staff. One hundred six patients with terminal renal insufficiency and 29 medical personnel were given three doses of hepatitis B vaccine at an interval of 0, 1, and 6 months (Merck, Sharp and Dohme, West Point, Pennsylvania, part of a joint study no. 649). Chronic hemodialysis patients (N = 99) received 40 μg vaccine (V) i.m. Uremic patients, who were just about to start chronic dialysis treatment (N = 7), were given 40 μg V, and at the first vaccination 3 ml hyperimmune globulin (HBIG) in addition. The medical personnel was alternately vaccinated with 20 μg V (N = 8), 40 μg (N = 11), 40 μg V, and 3 ml HBIG at the first vaccination (N = 10). After 12 months, 50% of the male dialysis patients, 66% of the female dialysis patients, and 95% of the medical staff developed anti-HBs antibodies. The anti-HBs titer of the dialysis patients was ten times lower than in the medical staff. The simultaneous passive immunization did not lead to any impairment of the anti-HBs titer in the dialysis patients and staff. The type of renal disease, length of time on dialysis, hematocrit, and immunoglobulin concentration did not influence the rate of immunization. After 12 months, 43 patients without antibody response were vaccinated a fourth time. Sixteen of these patients then developed anti-HBs, improving the immunization rate from 56.5 to 71.7%. A fifth vaccination only led to seroconversion, when brief or borderline anti-HBs could already be demonstrated previously. In dialysis patients who fail to develop anti-HBs after three doses of vaccine, a fourth vaccination is recommended after 12 months.

Vaccination contre l'hépatite B active de malades hémodialysés et du personnel medical. Un cent et six malades en insuffisance rénale terminale et 29 personnels médicaux ont reçu trois doses de vaccin antihépatite B à un intervalle de 0, 1, et 6 mois (Merck, Sharp et Dohme, partie d'une étude coopérative no. 649). Les hémodialysés chroniques (N = 99) ont reçu 40 μg de vaccin (V), i.m. Les malades urémiques, qui étaient juste au moment de commencer l'hémodialyse chronique (N = 7), ont reçu 40 μg de V, et à la première injection 3 ml de globulines hyperimmunes (HBIG) en plus. Le personnel médical était vacciné alternativement avec 20 μg de V (N = 8), 40 μg (N = 11), 40 μg de V, et 3 ml de HBIG à la première vaccination (N = 10). Au bout de 12 mois, 50% des hommes dialysés, 66% des femmes dialysées, et 95% du personnel médical ont développé des anticorps anti-HBs. Le titre des anti-HBs chez les hémodialysés était dix fois plus faible que dans le personnel médical. L'immunisation passive simultanée n'a pas entraîné de diminution du titre des anti-HBs chez les hémodialysés ou le personnel. Le type de maladie rénale, le temps passé en hémodialyse, l'hématocrite, et la concentration d'immunoglobulines n'ont pas influencé la vitesse d'immunisation. Après 12 mois, 43 malades sans réponse anticorps ont été vaccinés une quatrième fois. Seize de ces malades ont alors développé des anti-HBs, améliorant le taux d'immunisation de 56,5 à 71,7%. Une cinquième vaccination n'a entraîné qu'une séroconversion, lorsque des anti-HBs passagers ou limites pouvaient déjà auparavant être démontrés. Chez les dialysés qui n'ont pas développé d'anti-HBs après trois doses de vaccin, une quatrième vaccination est recommandée après 12 mois.

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Hepatitis B virus infection leads to chronic HBs antigen carrier status in 60% of uremic patients. This is accompanied by high infectivity as demonstrated by HBeAg in 70 to 90% of patients [1–3]. HBsAg-positive patients constitute a continuous risk of infection for the dialysis staff and their home environment. Immunogenicity and efficacy of hepatitis B vaccine were demonstrated in groups with high risk of infection, including homosexual men [4, 5], personnel of dialysis units [6, 7], and dialysis patients [8]. It was shown that the development of anti-HBs corresponds to protection from infection [7, 9]. Both vaccines were licensed in West Germany, and a rate of immunization of over 90% was found for healthy subjects in several investigations. In contrast, the rate of immunization of hemodialysis patients varies from 89% [10], 60% [8], and 62% [11]. In the present immunogenicity study (part of a multicentric investigation, study no. 649) the following questions were examined:

- What portion of dialysis patients are immunized and to what degree?
- Does simultaneous passive vaccination influence the active immunization process in patients with chronic uremia?
- What procedure is recommended in patients who do not show any seroconversion despite triple vaccination?

Methods

One hundred six patients with terminal renal insufficiency and 29 members of the medical staff were vaccinated with a hepatitis B vaccine (MSD, Merck, Sharp and Dohme GmbH, lot 802) developed by Hillemann et al [12]. Two intramuscular injections of hepatitis B vaccine at an interval of 4 weeks and a third injection after 6 months were given to patients and staff. Liver enzymes were normal and no hepatitis B markers were present in all patients. Patients, already on long-term maintenance hemodialysis (group 1, N = 99) received 40 μg vaccine (V) at each interval. Uremic patients, who were just about to start chronic hemodialysis treatment (group 2, N = 7), were likewise given 40 μg V and in addition 3 ml hyperimmunoglobulin (HBIG) at the first vaccination. Members of the medical staff

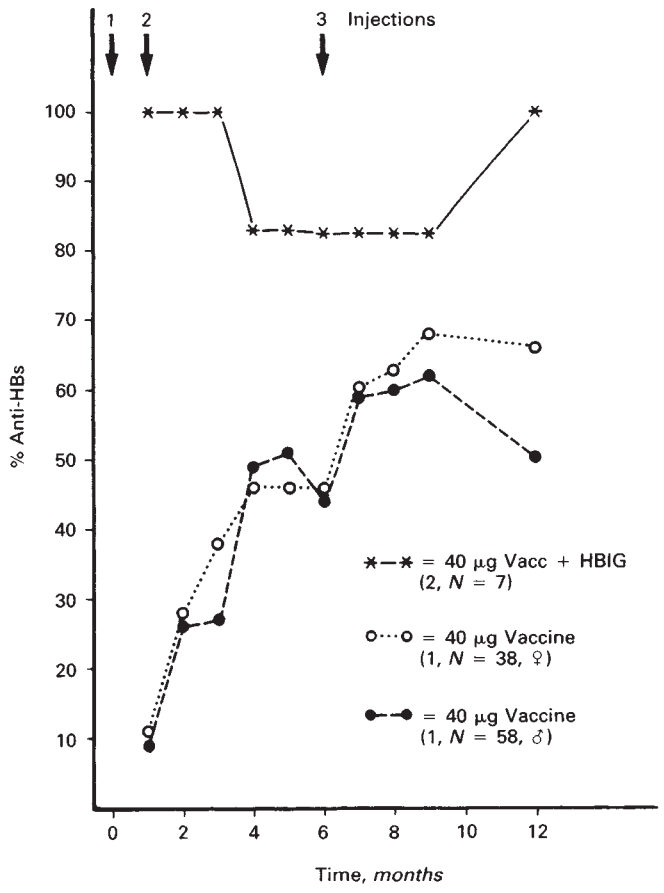

Fig. 1. *Immunization rate of patients with chronic uremia after triple hepatitis B vaccination.* Group 1 contains dialysis patients; group 2, patients about to begin chronic hemodialysis treatment.

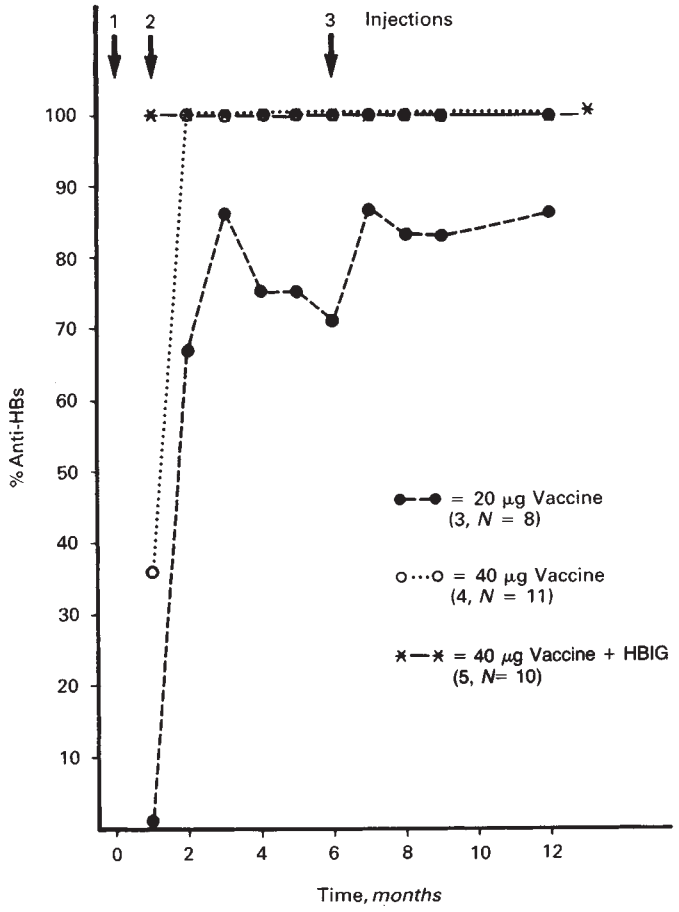

Fig. 2. *Immunization rate of medical personnel in the dialysis unit after triple immunization with different doses.*

were alternately assigned to group 3 (20 µg V, $N = 8$), 4 (40 µg V, $N = 11$), and 5 (40 µg V and in addition 3 ml HBIG at the first vaccination, $N = 10$). When no anti-HBs antibodies could be demonstrated after 12 months, a fourth vaccination was administered. If there was no seroconversion despite the fourth vaccination, a fifth vaccination followed 3 months later.

Laboratory controls were carried out twice before the beginning of vaccination and afterwards at intervals of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 18, 21, and 24 months. HBsAg (Auszyme), anti-HBc (Corzyme), anti-HBs (Ausab), HBeAg and anti-HBe (Abbott-HBe™) were determined with commercially available test systems (Abbott Laboratories, Chicago, Illinois). Sera with positive anti-HBs findings were tested in double dilutions to the endpoint. The limiting value was considered 2.1 times to control determinations. The individual persons were rated as positive when the fourfold limiting value was exceeded. Anti-HBs positivity or seroconversion was assumed in the individual patients and control group when anti-HBs antibodies could be demonstrated in two consecutive controls. The following laboratory values were determined each time: SGOT, SGPT, y-GT, alkaline phosphatase, total bilirubin, IgG, IgA, and IgM.

Results

Side effects. Fifteen patients reported the following symptoms: painful pressure at the injection site (1), fever (2), vomiting (5), nausea (2), fatigue (6), limb pains (1), headache (3), bladder pain (1), and neck pain (1). One staff member reported fatigue.

Deaths. Ten patients died during the observation period of 18 months. Three of these patients died within 12 months and were therefore not considered in the evaluation. The causes of death were: coronary heart disease with myocardial infarction (3) or arrhythmias (4), severe cerebral sclerosis (1), psychosis resulting in suicide (1), and interstitial pneumonia after kidney transplantation (1). None of the patients had an illness resembling the so-called acquired immunodeficiency syndrome ("AIDS").

Hepatitis B virus infections. During the entire observation period, a hepatitis B virus infection occurred only in one case. This patient, who did not show anti-HBs up to that time, developed a hepatitis B infection of mild course within 1 month after the beginning of vaccination with the occurrence of HBsAg, HBeAg, and a moderate elevation of transaminases, which remained below the triple normal value. Three months after the beginning of injection, all laboratory parameters had normalized. At the same time, anti-HBs, anti-HBe, and anti-HBc could be demonstrated.

Immunization rate. The male dialysis patients (group 1A) developed anti-HBs in 9% after 1 month (before the second vaccination), in 44% after 6 months (immediately before the

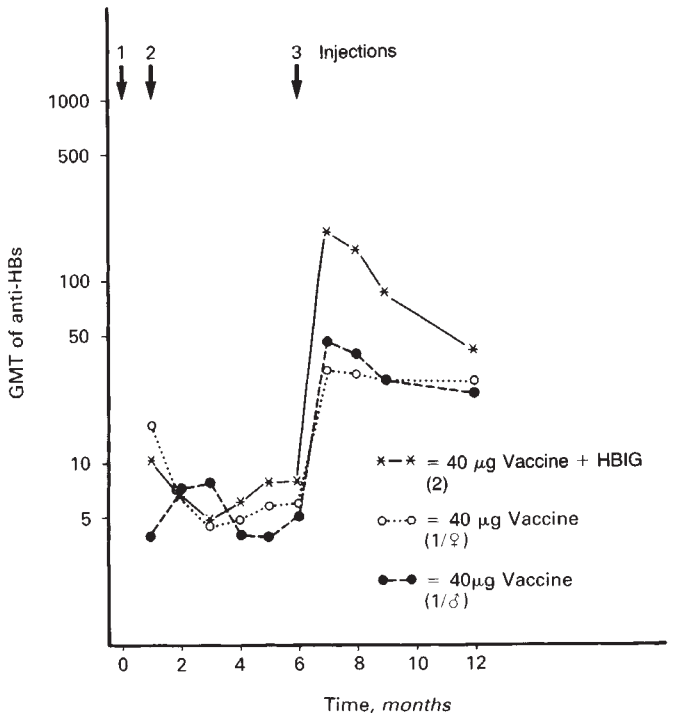

Fig. 3. *Anti-HBs titers in patients with chronic uremia.* GMT represents the maximum mean geometric titer.

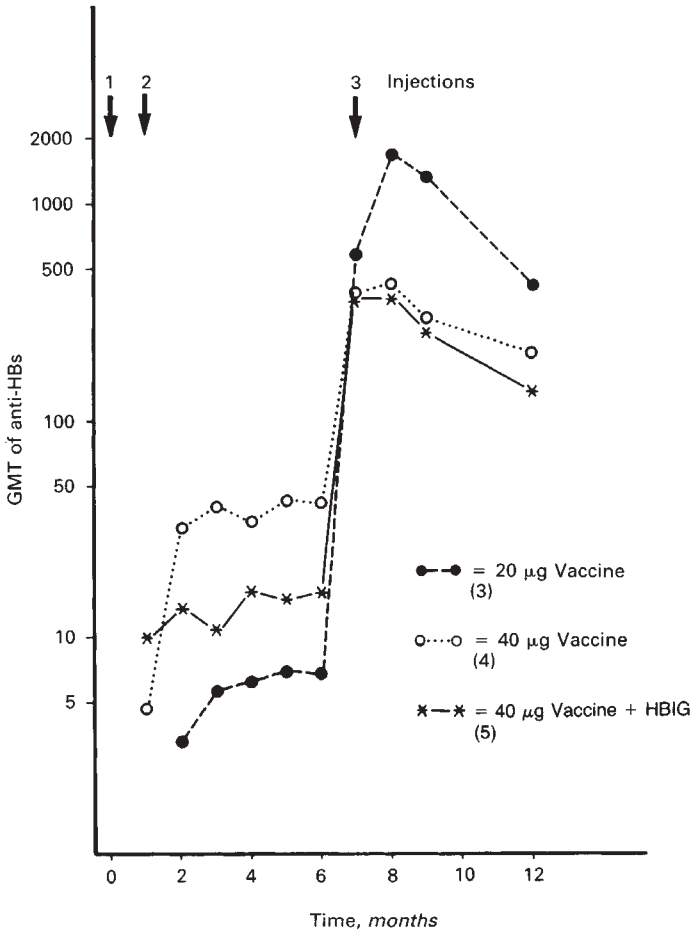

Fig. 4. *Anti-HBs titers in medical personnel of the dialysis unit.* GMT represents the maximum mean geometric titer.

third vaccination), and in 50% after 12 months. The immunization rates of the female dialysis patients (group 1B) were 11, 46, and 66%, respectively (Fig. 1).

Uremic patients (group 2), who were given simultaneous passive/active immunization for immediate protection before the beginning of the chronic hemodialysis treatment, all showed a seroconversion within 12 months (Fig. 1). In the control group of the dialysis unit staff (groups 3, 4, and 5), a high immunization rate was found independently of the vaccination scheme (20 μg, 40 μg vaccine, or 40 μg vaccine and 3 ml HBIG). Only in one patient did seroconversion not occur after administration of 20 μg vaccine (Fig. 2).

Anti-HBs titers. The third vaccination led to an abrupt rise of the anti-HBs titers which reached their maximum 1 to 2 months later, that is, in month 7 or 8. The maximum mean geometric titer (GMT) was 48.29 ± 1.23 in the male dialysis patients, and 32.38 ± 2.00 in the female dialysis patients (Fig. 3). Additional passive immunization of patients who were just about to commence chronic hemodialysis treatment (group 2) did not lead to any impairment of the anti-HBs titer which averaged 181.02 ± 8.23 after 7 months (Fig. 3). In the healthy control group, the medical staff, the maximum mean geometric titers were 1722.15 ± 1.63 (GMT) (group 3), 463.73 ± 40.3 (group 4), and 394.80 ± 1.55 (group 5). Compared to the dialysis patients, the mean maximum anti-HBs titers were roughly ten times higher in healthy subjects (Fig. 4).

Influence of sex, age, dialysis, hematocrit, kidney disease, and immunoglobulins on anti-HBs development. After 12 months, 66% of the female dialysis patients and 50% of the male patients had developed anti-HBs antibodies (NS). At the same time, the immunization rate decreased with increasing age in the male patients ($P < 0.01$). The mean age of male dialysis patients, who became anti-HBs positive, was 39.8 ± 11.8 years, and 52.8 ± 11.7 years, when no anti-HBs occurred. Anti-HBs was demonstrated in seven out of eight male dialysis patients under 30 years but only in one out of nine men over 60 years. This age-dependence could not be shown in females, where seven out of ten dialysis patients younger than 30 years developed anti-HBs as compared to six out of seven patients over 60 years. The mean length of time on maintenance dialysis and the hematocrit had no influence on the anti-HBs development. The kind of renal disease also did not influence the immune response to the hepatitis B vaccination with the possible exception of men, where those with chronic glomerulonephritis may have responded better (15+/8−). However, this tendency is not statistically significant. The immunoglobulin concentration of IgG, IgA, and IgM in the serum also was not correlated to the rate of immunization in either dialysis patients or in the healthy subjects.

Fourth and fifth vaccination of patients without antibody response. Forty-three patients in whom seroconversion had not occurred 12 months after the beginning of vaccination received a fourth injection. Anti-HBs then developed in 16 patients (37%). However, a brief or borderline anti-HBs reactivity had occurred in nine out of 16 patients during the prior 12 months,

whereas in seven patients there had been no prior reaction. Seventeen patients who did not develop anti-HBs after the fourth injection were vaccinated a fifth time. Only in three patients, seroconversion occurred from this fifth vaccination. In two of the three patients, a transient or borderline anti-HBs titer had occurred before.

Discussion

Immunization rate. Anti-HBs antibodies developed in over 90% of the medical staff after triple vaccination. This immune response rate was also shown for healthy subjects in other investigations [5–7, 13–15]. In the dialysis patients, anti-HBs occurred only in 56.5% (men 50%, women 66%). This poor immune response is likely due to an immune deficiency of patients with chronic uremia, which predisposes them to become chronic carriers of HBs antigen as well [16]. In two investigations, where another vaccine and vaccination schedule were used, a comparable rate of immunization with 62 or 60% of dialysis patients was reported [11, 8]. In contrast to these reports and to our own results, Stevens et al [10] found a much higher immunization rate totaling 89% (76% male and 100% female dialysis patients) with the same vaccine, dose, and schedule of vaccination. Our lower rate of immunization might be partially explained by our more restrictive definition of seroconversion, a hypothesis supported by the impressive increase of anti-HBs antibodies after a fourth vaccination in our patients.

In one study, female dialysis patients developed anti-HBs in a higher percentage than men [10]. However, in our investigation and also in the one by Crosnier et al [8], this sex difference was not statistically significant. The capacity to eliminate the HBs antigen in a higher percentage of female patients is to be regarded as an additional sign of a more pronounced immune response of women. In addition, a correlation between age and anti-HBs formation, which decreases markedly at a greater age, has been reported [8]. In our patients, this correlation was found only for male patients.

Simultaneous passive/active immunization. The simultaneous passive/active immunization does not lead to any impairment of anti-HBs formation in healthy subjects [14, 15]. In our investigation, this was also shown for patients with terminal renal insufficiency. Immunization rate and anti-HBs titer of chronic uremic patients did not differ in simultaneous passive/active immunization compared to active immunization alone. However, the number of simultaneously vaccinated patients is too small for a definitive appraisal. In addition, the two groups differed to the extent that the simultaneously passive/active vaccinated were still being treated conservatively and were just about to start chronic hemodialysis, whereas the active who were vaccinated had already been hemodialyzed for months or years. Despite this limitation, a simultaneous passive/active vaccination can be recommended in healthy subjects and also in patients with chronic renal failure in all situations which require an immediate protection. In patients with chronic uremia, this problem primarily arises at the beginning of chronic hemodialysis treatment.

Procedure in patients without antibody response. In patients who did not show anti-HBs antibodies after 12 months, a fourth injection then led to the appearance of anti-HBs in 37% of the patients. If seroconversion did not occur after the fourth vaccination, then a fifth vaccination was only successful in three patients, two of whom had shown a brief or borderline occurrence of anti-HBs antibodies within the previous 12 months. In dialysis patients without antibody response after three doses of vaccine usually suggested, a fourth vaccination is recommended, which may be instituted 12 months after the onset of the vaccination schedule. If seroconversion does not occur despite the fourth vaccination, a schematic fifth vaccination no longer appears to be worthwhile. A fifth vaccination appears to be successful only when there has been prior transient or borderline anti-HBs development. An alteration of the vaccine dose or the vaccination schedule has to be considered for this group of patients.

Patients who only develop anti-HBs antibodies after the fourth or fifth vaccination will probably require a booster vaccination; this is planned for 6 months later. The suitable time interval cannot be definitely fixed at the present time. With a fourth vaccination, the immunization rate rises from 56.6% to a total of 71.7% in dialysis patients. To attain a higher immunization rate, comparable with that of healthy subjects, in prospective dialysis patients, the hepatitis B vaccination should be carried out as soon as possible in the course of a kidney disease, that is, before commencement of uremia with its disturbed immune reaction.

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