Intracutaneous versus intramuscular hepatitis B vaccination in primary non-responding haemodialysis patients

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Abstract

Objective. To determine whether hepatitis B vaccination given intracutaneously (IC) is more effective than intramuscularly (IM) in primary non-responding haemodialysis patients.

Design. A prospective, randomized study of antibody responses to hepatitis B vaccine given IC or IM, in 25 haemodialysis patients. Outcome measures were rates of seroconversion, mean and geometric mean levels of antibody achieved, and antibody levels 1 year after vaccination.

Results. With a dosing schedule of 10 μg vaccine once a week IC in the skin overlying the deltoideus muscle of the non-dominant arm during 12 consecutive weeks, antibody levels to hepatitis B surface antigen (anti-HBsAg) of 10 IU/l or more were achieved in nine of 10 evaluable patients, with a geometric mean of 70 IU/l. Nine months after the end of the vaccination anti-HBsAg levels had dropped to 9±4 IU/l (M±SE), with a geometric mean of 5 IU/l, in the nine remaining evaluable patients.

With a dosing schedule of 40 μg vaccine i.m. in the deltoideus muscle of the non-dominant arm at 0, 1, and 3 months, anti-HBsAg levels of at least 10 IU/l were achieved in eight of 14 evaluable patients, with a geometric mean of 94 IU/l. Nine months after the end of the vaccination anti-HBsAg levels had dropped to 16±7 IU/l, with a geometric mean of 9 IU/l, in the nine remaining evaluable patients. Anti-HBsAg levels at 8 and 12 weeks were higher in the IC than in the group receiving vaccine IM (at 8 weeks 134±76 vs 39±20 IU/l, P<0.05, and at 12 weeks 188±98 vs 47±18 IU/l P<0.01). The half-time of anti-HBsAg is about 13 weeks, both when the averaged absolute and when the geometric mean levels are used for the estimate.

Conclusion. The intracutaneous route is a less practical but effective method of vaccination against hepatitis B in primary non-responding haemodialysis patients. The weekly 10 μg vaccine IC scheme resulted in the fastest development of protective antibody levels, within 8 weeks, which may be useful in previously non-immune persons who may be infected with hepatitis B virus (e.g. needle-stick accidents).

Key words: hepatitis B; vaccination; non-responders; haemodialysis; intracutaneous; intramuscular

Introduction

Haemodialysis patients with an absent response to hepatitis B vaccine, estimated between 20 and 40% [1–3], have the highest risk of hepatitis B disease. The first reports about the intradermal route of vaccination did not show a high seroconversion rate; however, these studies used relatively low doses [4,5]. Recently 70–100% seroconversion rate was reported in haemodialysis patients with the intradermal route of administration [6,7]. We investigated in a prospective randomized way in haemodialysis patients who previously had not responded to a standard vaccination scheme against hepatitis B virus, whether the intracutaneous route of administration (IC) is more effective than the intramuscular route (IM). We compared 12 weekly 10-μg doses (0.25 ml) IC to three 40-μg doses IM in order to compare exactly the same cumulative dose. The antibody levels were followed for 1 year to determine the rate of decline in the two groups.

Subjects and Methods

Patients and vaccination scheme

Twenty-five haemodialysis patients were selected from three dialysis centres on the basis of having not responded, i.e. antibody titres always remaining below 10 IU/l, to at least one regular hepatitis B vaccination scheme. This regular vaccination scheme consisted of four 20 μg doses of recombinant hepatitis B vaccin (Engerix, SmithKline Beecham, The Netherlands), given at 0, 1, 6, and 12 months IM. None of the patients had detectable anti-HBsAg antibodies or was positive for HBsAg. All patients except one were negative for antiHepC antibodies. The study protocol was approved by each hospital's medical ethics committee. After informed

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consent was obtained, the patients were randomly allocated, in each hospital in blocks of four, to an IC or an IM vaccination scheme. In all patients hematocrit values were kept between 30 and 35% using erythropoetin treatment.

The IC scheme consisted of 12 doses of 10 µg hepatitis B vaccine (HepB-DNA, 40 µg/ml, Merck, Sharp & Dohme, Haarlem, The Netherlands), given 1 week apart over the course of 12 weeks, in the skin overlying the deltoideus muscle of the non-dominant arm, using 21-gauge needles and an intracutaneous puncture trajet of about 5 mm.

The IM scheme was three doses of 40 µg of the same hepatitis B vaccine at time 0, 1, and 3 months, given intramuscularly in the deltoideus muscle of the non-dominant arm.

Analysis and assay

Antibodies against hepatitis B surface antigen were detected using a standardized microparticle Elisa (IM-X, Abbott Inc., North Chicago, Illinois).

Results are presented as means ±SEM and as geometric mean values. A $P$ value less than 0.05 defined statistical significance. Two-way analysis of variance on the measured values was used to examine differences between the two groups.

Results

Eleven patients were randomized to the IC protocol: seven males and four females, mean age 61.4±4.5 years and weight 64.3±3.4 kg. One patient died before the first blood sample after the start of vaccination could be taken. This patient was not included in the analysis, leaving 10 patients for further evaluation. One patient died 49 weeks after the start of this protocol. Nine of these 10 patients (90%) reached anti-HBsAg levels of at least 10 IU/l, with a geometric mean of 70 IU/l. Anti-HBsAg levels at 8 and 12 weeks were higher than in the group receiving vaccine IM (at 8 weeks $134±76$ vs $39±20$ IU/l ($P<0.05$) and at 12 weeks $188±98$ vs $47±18$ IU/l ($P<0.01$), see Figure 1). One year after this vaccination scheme the average anti-HBsAg level was $9±4$ IU/l, with a geometric mean of 5 IU/l.

Fourteen patients were randomized to the IM protocol: nine males and five females, mean age 59.6±4.4 years and weight 65.3±5.0 kg. Two patients died, from unrelated diseases, at 11 and 23 weeks and two received a kidney graft at 4 and 31 weeks after the start of this vaccination scheme. All samples of these four patients that were collected, were included in the analysis. Eight of these fourteen patients (57%, $P=0.09$) reached anti-HBsAg levels of at least 10 IU/l, with a geometric mean of 94 IU/l. One year after this vaccination scheme the average anti-HBsAg level was $16±7$ IU/l, with a geometric mean of 9 IU/l.

The maximum anti-HBsAg level reached was not significantly different between the IC and the IM group. The time course of the average and geometric mean anti-HBsAg levels in the two groups are depicted in Figure 1. The half-time of anti-HBsAg is about 13 weeks. Only minor (local pain and/or erythema) side-effects were noted in either vaccination scheme.

Discussion

In this study we compared an intracutaneous with an intramuscular scheme of vaccination in previously non-responding haemodialysis patients. This was done in a randomized prospective manner, and to optimize the comparison the exact same cumulative dose of vaccine was given within the first 3 months and anti-HBsAg levels were followed for 1 year. Interestingly, as described by others [6], the intracutaneous scheme resulted in a faster antibody response than the intramuscular scheme. Already at 8 weeks, when in the IC scheme 70 µg of vaccine and in the IM scheme 80 µg of vaccine had been administered, the geometric mean anti-HBsAg level was 32 versus 3 IU/l in the IC vs the IM scheme (means $134$ vs $38$ IU/l).
Vaccinating non-responding haemodialysis patients

This suggests that this IC scheme may be useful in needle-stick accidents when a non-immune person accidentally is infected with HBsAg-positive material.

We observed a further rise in anti-HBsAg levels 1 month after the end of the vaccination schedules. Thereafter the levels decreased in all patients, with an estimated half-time of 13 weeks. From this half-time and the level of anti-HBsAg after the last vaccination dose, it can easily be estimated when a patient will reach a level below 10 IU/l, at which time a booster dose seems indicated to maintain protective antibody levels [8]. Our data suggest that an exact scheduling of anti-HBsAg level determination is not important, as long as it is at least 1 month after the last dose of vaccine given.

The incidence of hepatitis B virus infection is declining considerably [9,10]. In the USA, the incidence of HBsAg positivity in haemodialysis patients has declined between 1975 and 1992 from 3.0 to 0.2% and among dialysis centre staff from 0.9 to 0.04% [10,11].

The prevalence of HBsAg positivity also declined, from 7.8 to 1.3% among patients and from 0.9 to 0.3% among staff members [10,11]. Meanwhile the presence of antibody to HBsAg increased in patients from 12 to 21% among patients and from 18 to 53% among staff, and was significantly related to the levels of hepatitis B vaccine coverage [10,11].

The increase in vaccine-induced antibody response to hepatitis B virus surface antigen, a decrease in virus prevalence, together with improved hygienic measures have contributed to the decline in new hepatitis B virus infections. Due to this declining incidence and prevalence, cost-benefit analysis of preventive vaccination programmes, depending on local endemicity, may turn out relatively costly [12]. In view of the morbidity and mortality rates of hepatitis B disease and the costs relative to that of dialysis treatment, however, preventive vaccination against hepatitis B virus remains strongly recommended [3].

It is concluded that the intracutaneous route is a less practical but at least equal effective method of vaccination against hepatitis B in primary non-responding haemodialysis patients. Our weekly 10-μg vaccine IC scheme resulted in the fastest development of protective antibody levels.

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References


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