IS PASSIVE IMMUNISATION AGAINST HEPATITIS B A LUXURY, DANGER OR NECESSITY FOR DIALYSIS PATIENTS AND STAFF?

H C Burck, P Berg*

Abteilung für Intensivmedizin und Dialyse, Städt. Krankenhaus, Kiel, and *Abteilung Innere Medizin II, Medizinische Universitätsklinik, Tübingen, GFR

Summary

Out of 91 patients and staff members in a hospital dialysis and a limited care dialysis unit 20 patients and 18 staff members with a negative test for anti-HBs were passively immunised against hepatitis B using an immunoglobulin enriched by Cohn’s fractionation. Twenty-two anti-HBs-negative patients on holiday dialysis were excluded and dialysed in a separate room. Eleven HBsAg-positive patients were dialysed at the same time in both units, under special care. After nearly two years of observation no staff member contracted hepatitis B, while prior to the study 3 of 8 nurses had hepatitis B. Five patients acquired hepatitis B during the two years; out of 22 holiday guests two developed hepatitis and are now carriers. One patient, who was not immunised because of a false positive anti-HBs test, contracted hepatitis. Two patients suffered from hepatitis B in spite of passive immunisation and two similar observations have been reported elsewhere. One of our patients died from acute liver failure. The question as to whether the administration of immunoglobulin during the incubation period has a deleterious rather than a beneficial effect cannot yet be answered. We conclude that the supposed protection was effective especially since one unit became free from hepatitis, and immunisation could be stopped. Patients and staff members should be immunised only in infected units.

Introduction

Hepatitis B infection and prevention have always been major problems in dialysis patients and kidney transplantation. Therefore the EDTA Registration Committee has paid much attention to this in all past reports [1–5]. From last year’s report [4] we learned that 75.5% of hospital and 87.1% of home dialysis patients were HBsAg negative. This means that more than 5,000 of the 27,343 living dialysis patients contracted hepatitis and 298 of them died from this infection (2.9%). According to this year’s report, within the 12 years now covered by the Registry 4,593 staff members acquired hepatitis B. Sixty-
five nurses and doctors paid for their services to dialysis patients with their lives. Any possibility of reducing this risk to patients and staff must be tried.

The data from 1977 in this volume contain the latest results of all living 22,830 patients on hospital dialysis: 76.5% always had a negative test for HBsAg. Only 183 of all patients on hospital dialysis had antibodies due to 'active' immunisation and only 570 patients were passively immunised. 'Active' immunisation with vaccine from HBsAg-positive carriers is still in the experimental stage and unsatisfactory [6,7]. Immunoglobulins for passive immunisation, until now prepared only by some study groups [8–10], recently became commercially available.

In contrast to Delons and co-workers [11], who immunised only the 57 staff members of a dialysis unit, we started to protect patients and staff members two years ago using a similar immunoglobulin rich in HBs-antibodies.

Materials and Methods

At the time we started this programme the situation was rather threatening. All 15 patients of a newly installed dialysis unit contracted hepatitis B within 4 years. Six of them did not convert to HBsAg-negative. One died from chronic hepatitis after three years. Three of eight nurses contracted hepatitis B and one became a carrier.

Ninety-one patients and staff members of the hospital dialysis centre and of a limited care unit were studied. Twenty patients and 18 staff members with negative tests for HBsAg and anti-HBs were immunised. For six patients no further immunisation was necessary because they were transplanted or had moved, and one older patient had died from heart failure. Five patients were removed from regular immunisation, since all HBsAg-positive patients were grouped in the limited care unit during the course of the study and the hospital dialysis unit stayed free from carriers. At the time of presentation of these data only 7 out of the 20 patients and 5 out of the 18 staff members were being kept in the immunisation programme; 6 staff members left the programme because they terminated employment and for 7 members protection was stopped, since there were no HBs-carriers left in the unit.

Fifty-three patients and staff members were excluded from immunisation: 22 sero-negative patients because they were only on holiday dialysis and were treated in a separate room; 4 staff and 9 patients because of positive tests for antibodies; 11 patients in both units because of persistently positive tests for HBsAg. After one unit had become free from carriers seven newly accepted patients were excluded from the programme.

The immunoglobulin used was fractionated by the Cohn ethanol method [8–12]. Fraction II and II/III were combined and a final protein concentration of 16% was achieved by ultrafiltration. Sera were taken from convalescents with a minimum titre of 1 : 4,000 and pooled. Antibody content was controlled during and after fractionation by the producer by the Ausab-test and were confirmed by our own measurements using the same method. With the exception of 1 batch prior to commercial selling the antibody titre was at least 1 : 20,000 per ml (Gammaproct-Hepatitis ®, Fa.Biotest).
Figure 1 demonstrates the immunisation intervals. After a starting period using a 6 week and a 2 month interval it became apparent from regular control of antibody titres during the period with 3 and 4 month intervals, that bimonthly periods were necessary to maintain adequate antibody levels. Since April 1978 intervals have been calculated from the individual half-life time of the immunoglobulin.

Dialysis patients were injected one hour prior to a dialysis, but local haemorrhage was never observed. Patients were on 3 x 4 hours/week dialysis schedule with a Drake-Willock Machine and capillary dialysers. There were separate rooms for HBsAg-positive patients.

The study was not randomised since we considered it unwise to exclude patients or staff members from a protective procedure which we assumed to be effective.

Results

Anaphylactic or other allergic reactions were never observed after more than 150 immunoglobulin injections. Local pain at the site of injection in the M. glutaeus is frequent, but mild and disappears within a few hours.

Because of frequent changes among the staff only six individuals have been immunised regularly over the complete period. In spite of this none of the 18 staff members contracted hepatitis B serologically. After a period of 15 months there was no case of hepatitis B among 12 patients in a unit, where previously HBsAg-positive patients were treated. Six months after termination of immunisation for patients and staff there is no case of hepatitis B nor any carrier in this unit.

Six of eight patients in the limited care unit stayed free from hepatitis B, although 11 patients are persistently HBsAg-positive.

In total we saw five cases of hepatitis during the immunisation campaign. Out of 22 anti-HBs-negative dialysis patients who had not been passively immu-
nised and had been dialysed for 2 to 6 weeks during holidays, two developed hepatitis B and are now carriers. One patient, who was not immunised because of a positive test for antibodies, nevertheless contracted hepatitis B. A second analysis of the original sera which had been frozen prior to the study, revealed that there were no detectable antibodies.

Out of 38 persons under observation, two patients contracted hepatitis B in spite of passive immunisation and one of them died within 30 days from acute liver failure.

Comment

In addition to our two cases who acquired hepatitis B in spite of passive immunisation, Dr Frohner in Vienna (personal communication) has observed two similar patients. Both had received immunoglobulins of the same preparation as our group at least once during the three month incubation period. Our two patients had been injected with immunoglobulin 4 weeks and 2 weeks respectively prior to the first positive result for HBsAg. The four patients have in common that prior to the hepatitis there were at least two negative anti-HBs tests at the end of the immunisation period. However, 12 other patients and staff who also had undetectable antibodies at the end of an immunisation interval did not acquire hepatitis B.

Since it has been shown by several groups [12,13] and was confirmed by our follow-up study and measurements, that there is a large individual variation in the half-life time of immunoglobulin, it seems reasonable to suppose that persons with a high turnover rate lose their protective titre. Therefore control measurements within shorter periods are mandatory to adjust immunisation intervals to the individual disappearance rate of antibodies.

Since it has not been elucidated so far whether other factors, like cellular immunity, may be involved in the protection against hepatitis B [14], we cannot expect that passive immunisation will be effective to the extent that it will eliminate the hepatitis problem completely. In this respect it has to be stressed that uraemic patients react differently immunologically from healthy persons [13,15]. The observation that one of our patients, who was immunised during the incubation period, died from severe hepatitis raises the question whether the application of immunoglobulin had a deleterious rather than a beneficial effect. However, no similar course was observed and the three other patients in this situation survived. Theoretically it seems possible that anti-HBs-antibodies may interfere with the immunoregulatory processes during the incubation period thereby altering the immune response. Any similar observation needs to be carefully recorded in order to exclude this possible immunological mechanism and to make sure that passive immunisation during the incubation period does not increase the risk of fatal hepatitis B infection.

Conclusions

Immunoglobulins with a high concentration of HBs-antibodies are protective against hepatitis B for patients and staff members in dialysis units. Therefore
patients and staff ought to be passively immunised against hepatitis B, but only in infected units. The immunisation sera should have a standardised titre of at least 1:20,000 per ml, and 5 ml have to be administered. Because of individual variation of half-life, titre control is mandatory at least at monthly intervals. Immunisation has to be repeated at least every three months. If there is a faster drop of serum titre, the intervals have to be reduced to two months or even less.

Acknowledgment

The study was supported by Fa. Biotest-Serum-Institut, Frankfurt.

References

8 Krugman, S, Giles, JP and Hammond, J (1971) JAMA, 218, 1665
14 Eddleston, ALWF and Williams, R (1974) Lancet, ii, 1543
15 Vischer, TL (1971) Allergy, 15, 268

Open Discussion

WING (London) We have had horrible experiences with hepatitis in the UK and lost staff, but the picture now is much more encouraging and the improvement has been brought about, not by immunisation, but by the application of epidemiological methods; by selection of patients, by screening of blood products and other methods to prevent cross infection. Now that you have got some of your units clear, obviously the application of these classical methods will be extremely important. I do not know if we are particularly fortunate in the UK in relation to the rest of Europe in terms of other methods for dealing with cross infection, perhaps vectors we do not have, but at any rate our success should encourage other countries to follow us in this respect. I refer you to the paper

BURCK This approach does not rule out the epidemiological procedures, but is useful if you want to clear a 'yellow' unit.

KERR (Newcastle) Dr Burck's results are very impressive and I would not like the fear of giving this material in the incubation period to deter others from using it. There have been many controlled trials of immunoglobulin in hepatitis A with no evidence at all that giving it late in the incubation period has any adverse effect. There was no adverse effect from this material, or similar material, in the American Fulminant Hepatitis Trial or in the Chronic Hepatitis Trial in the UK, so it seems to me rather unlikely that you produce an adverse effect from giving immunoglobulin during incubation.

KOPP (Munich) Hyperimmune globulin is of course highly expensive; now are you aware of any trials where just normal immune globulin has been administered, particularly at repeated monthly intervals over the long incubation period of hepatitis B, because it has been reported that preliminary experience was simply too short and failures of protection from hepatitis B by low titre globulin was simply due to the early cessation of repeated immunisation. One has to give it over at least six months.

BURCK I think the application of an ordinary immunoglobulin and its effect on protection against hepatitis is dependent on the pooling of sera. There are some countries with a very high incidence of hepatitis B, especially in Africa, and you can have pooled sera which have quite high antibody titres. Maybe these immunoglobulins will be effective if you inject them at very short intervals. But to get a sufficient protection for patients and staff you need sera with a high antibody content as we use them with pooled sera from convalescents.