An Attempt to Prevent Hepatitis B in a Haemodialysis Unit's Team Utilisation of Specific Immunoglobulins

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Summary

From November, 1972 to November, 1974 the members of the team of a haemodialysis unit were systematically given Australia antigen immunoglobulin protection. Only one case of hepatitis occurred among the 53 members treated. The value of the antibody is discussed.

Introduction

Haemodialysis centres in France lead those of Europe in the frequency of hepatitis B infections in staff, according to a 1973 EDTA report. This is undoubtedly due to the high incidence of Australia antigen (Ag HB) in the patients under treatment. Our centre is no exception — from October, 1969 to November, 1972, during which 92 patients were being treated, 28 cases of hepatitis B occurred among staff. Since November, 1972, we have attempted to protect our personnel with repeated injections of specific anti-hepatitis B immunoglobulins (Ig G HB).

Results of this prophylactic treatment during the period from November 1972 to November 1974 are presented and discussed.

MATERIALS AND METHODS

All investigational work concerning Ag HB and HB antibodies (Ac HB) in both patient and staff sera was done at the Centre National de Transfusion Sanguine (CNTS) in Paris. Techniques utilized beginning in 1969 were immunodiffusion
(ID), electroimmunodiffusion (EID), complement fixation, immune adherence, and passive haemagglutination (HA). In addition, radioimmunoassay (RIA) was performed systematically beginning in 1972.

The antigen found in the large majority of patients was of Le Bouvier's sub-specificity a_y, corresponding to Soulier's a_2 3 Y. One patient was a_2 d (W), while four children from a paediatric service were a_3 d (W). All of the infected personnel were found to have subtype a_2 3 Y (W).

Anti HB immunoglobulin (Ig G HB) was prepared by the CNTS from a pool of plasma obtained from volunteers having HB antibody titres ranging from 1/1 to 1/2 as determined by the Ouchterlony immunodiffusion method. Plasma was fractionated by the Cohn ethanol method. In the final preparation, Ig G HB titre was 1/8 measured by ID and EID, 1/16,000 by HA, and 1/5,000 by RIA.

Subspecificities anti a, anti d and anti y were present in all preparations, with anti a predominating and anti y the scarcest. Absence of Ag HB was confirmed using highly sensitive techniques (RIA, HA), and no virus-like particles were observed on electron microscopy.

Ig G HB was stored in 5 ml vials and administered intramuscularly. Using 60 kg as an estimation of mean subject weight, the average dose was 0.08 ml/kg. The mean subject age was 28 years.

Description of the Population

The hepatitis 'epidemic' is considered as the 36-month period during which 28 staff members contracted this disease. This report includes only those persons, both staff and patients, who were in the centre for a period of more than three months. (The centre, which opened in 1969 with four dialysis units, now has 23 units and treats 70 patients.)

The percentage of HB carrying patients varies from 40 to 60%, and this has been taken into account by calculating the risk of contamination as a function of the number of patients actually carrying Ag HB. This risk has remained constant throughout the course of the study. Table I shows the number of dialyses performed, the number of persons exposed to the risk, and the number of contaminated dialyses. In the first period considered (18 months) only routine precautions typically associated with the aseptic handling of disposable materials were taken. In the second period, we attempted to protect overtly contaminated individuals with a single injection of a 5 ml dose of Ig G HB. Sixteen were treated in this manner.

Systematic Prophylaxis Procedure

Beginning in November 1972, all staff members exposed to a contamination risk were included in a protection programme. This group (57 people) included
doctors, nurses, nurse’s aides, and housekeeping staff. Excluded from the programme were all those who had previously contracted hepatitis B.

<table>
<thead>
<tr>
<th>TABLE I. Epidemiologic Situation</th>
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<tr>
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<tr>
<td><strong>Contaminated Dialysis</strong></td>
</tr>
<tr>
<td>I a (1969–1971)</td>
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<tr>
<td>I b (1971–1972)</td>
</tr>
</tbody>
</table>

The programme was as follows:

(1) All persons having neither Ag HB nor HB antibodies received a 5 ml injection of Ig G HB every 5 weeks during a 6-month period, and every 2 months thereafter. After 2 years of treatment, frequency of injections was reconsidered.

(2) Persons having antigen but not antibody did not receive treatment. One black person was in this category.

(3) Persons having measurable antibody did not receive treatment.

(4) The presence of antigen was to be determined before each injection, while antibody titres were to be measured only every 3 months.

After six months, the following modifications were adopted:

(1) Antibody titre was measured before each Ig G HB injection.

(2) Injections were discontinued in subjects attaining a minimal HB antibody level. This level was arbitrarily fixed as being equal or superior to 1/8 as determined by HA, antibody presence being confirmed by RIA.

The study was not randomized since we considered it unwise to continue the exposure of any staff to this potentially lethal risk.

**RESULTS**

The Ig G HB injections were administered according to the above routine. A high turn-over among staff members brought a large number of people into the treatment programme for less than 2 years. In consequence 80 were treated for less than 2 years while 30 were treated for more than 2 years.

Four persons displayed a local allergic reaction at the injection site. In the case of a nurse who suffered an anaphylactic reaction in the 18th month of treatment, it was necessary to discontinue injections.

Two of the 16 people treated with Ig G HB therapy following accidental
contamination during the second period contracted hepatitis; one at three weeks and the other at six months after injection. These are included in the 28 cases from the pre-prophylactic period.

Once systematic protection was initiated, from November, 1972 to November, 1974, only one case of hepatitis occurred in the particular circumstances which are summarised in Table 2. The affected nurse had received only 2 injections of Ig G HB, since she apparently had sufficient antibodies. However, when assayed 6 months after the last injection, anti-HB antibodies were no longer detectable. Unfortunately, she had left the service before receiving the indicated Ig G HB injection and contracted hepatitis one month later.

TABLE II. Comparison of Data during Epidemiologic situation and during the Protection Programme period

<table>
<thead>
<tr>
<th></th>
<th>Contaminated Dialysis</th>
<th>Exposed Personnel</th>
<th>Antibody Treated</th>
<th>Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (1969–1972)</td>
<td>5656 (39.7%)</td>
<td>67</td>
<td>0</td>
<td>28 (41.8%)</td>
</tr>
<tr>
<td>II (1972–1974)</td>
<td>5392 (39.8%)</td>
<td>57</td>
<td>57</td>
<td>1 (1.7%)</td>
</tr>
</tbody>
</table>

Nonetheless, Ag HB was detected in her blood for only a brief period (less than 15 days) and there was rapid normalization of the serum transaminases.

In Table III, which summarises antibody induction in treated subjects, it can be seen that only 10 people spontaneously reached the level of immunoglobulins considered sufficient by our programme.

TABLE III. Evolution of Antibody to HB Rate among the Team. (Presence in haemodialysis unit > 3 months)

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1/2</th>
<th>1/4</th>
<th>1/8</th>
<th>1/16</th>
<th>1/32</th>
<th>1/64</th>
<th>1/128</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without Antibody Protection</td>
<td>14</td>
<td>2*</td>
<td></td>
<td>1*</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Injection of Antibody when Infection Detected</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Systematic Protection with Antibody</td>
<td>47</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

* Members of the team having been > 3 months in another haemodialysis unit with the same outbreak conditions.

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DISCUSSION AND CONCLUSIONS

Of the two important conclusions to be drawn from our observations, the first is that the use of specific immunoglobulins as a therapeutic measure after overt accidental exposure to HB is only partially effective, since 2 persons out of 16 thus exposed and treated contracted hepatitis. However, both of these cases merit further discussion due to their unusual time-course. (See Figure 1)

Figure 1. Hepatitis since Systematic Protection

In one case, clinical symptoms appeared only 3 weeks after accidental exposure and subsequent Ig G HB injection, thus indicating the possibility of previous infection, since this is much shorter than the normal incubation period for HB. In the other case, the symptoms appeared 6 months after the accident. We feel that this person was in fact adequately protected by the Ig G HB injection, and that his eventual illness might have been due to a later undetected contamination.

It should be pointed out however that Krugman et al (1971) described a patient with a retarded incubation period of 5.5 months after being protected with Ig G HB. In addition, our only hepatitis case since the initiation of systematic protection occurred six months after that subject's last Ig G HB injection,
even though antibodies had been present two months after the injection. The problems posed by the interpretation of these cases have led us to establish a minimal antibody level for our programme, namely 1/8 measured by HA, in association with a positive RIA.

Secondly, as has already been discussed (Almeida, 1971; 1972; Szmuness, 1974), one must recognise that there are many possible routes of infections in a haemodialysis unit, and the risk of infection should be quantitated.

When a subject is accidently pricked with a needle contaminated with HB positive blood, parenteral exposure is estimated to be low (Soulier et al, 1972) However, infection via the digestive or respiratory systems could explain the hepatitis epidemic experienced in our unit before systematic protection was initiated.

Our favourable results with systematic therapy corroborate earlier reports of the effectiveness of specific immunoglobulins. Direct comparisons of results are difficult, however, due to differences in programme and ultimate objectives.

Prince, Krugman and Szmuness all used immunoglobulins prepared from hemophiliac serum, which has an elevated antibody titre. On the other hand, the serum used in the present study which was the same as used by Soulier et al (1972) has a titre 2.5 times weaker.

Prince et al (1971) tested the effectiveness of immunoglobulins by inoculating institutionalized children who were exposed to a high risk of infection via the digestive and parenteral routes; 2 out of 17 presented a moderated elevation of transaminases. Krugman et al (1971) first inoculated his subjects with a weak dose of the virus to stimulate accidental infection, followed by a single injection of immunoglobulins. Under these conditions, 70% of the subjects were protected.

Szmuness et al (1974) also studied institutionalized children living in a contaminated environment, repeating Ig G HB injections at four months intervals. The protective value of specific and non-specific immunoglobulins were compared in this series of experiments. The results were favourable and statistically comparable, but this is not surprising since the non-specific immunoglobulins also contain anti-HB antibodies, although at very low titres.

There are still many unknown factors concerning the appearance and significance of antibodies in protected subjects. We have interpreted the presence of antibodies appearing after two months as active antibodies. The highest titres attained appear either spontaneously or after a single injection of immunoglobulins.

Since the great majority of subjects are effectively protected without the induction of antibodies, it seems evident that an additional mechanism may be involved in the immunity against hepatitis B. Supporting this hypothesis, the work of Reed et al (1974) demonstrates the existence of cellular immunity much more widespread than that detected simply by antibody measurement.

Although our systematic protection plan may seem somewhat excessive for certain subjects from a theoretical point of view, its effectiveness in eliminating the hepatitis B epidemic among centre personnel is convincing and worth reporting.

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References

Almeida, J D (1972) *British Medical Bulletin*, 28

Open Discussion

D KLEINKNECHT (France) During the last year 25—40% of our patients were Australia antigen positive. All dialysis staff members at risk, including nurses and physicians, received specific gammaglobulin prepared by the same centre as Dr Delons' in Paris. Australia antigen and Australia antibody were absent in all members and none had a previous history of hepatitis. The staff included eleven permanent members and nine occasional members who received specific gammaglobulins for periods ranging from six months to one year. Dosages injected varied from 0.06—0.2 ml/kg every five weeks. Australia antigen was checked every two months. In none of these 20 members was Australia antigen found nor did hepatitis occur. In none did Australia antibody appear later. These results may confirm on a small series with a small period of time the findings of Dr Delons regarding the protective effect of passive immunisation with specific anti-Australia gamma-globulins used in our unit.

D G OROPOULOS (Canada) Am I right that controls were not studied during the same period as the test group?

DELONS I had two periods, before and after systematic prevention. We did not have two groups during the same period.

OROPoulos Could this mean that your findings are just a natural evolution of the disease since you showed us that there are some people who developed spontaneous immunity?

DELONS If you are right, another 35 cases would have occurred in the second period, but they did not.