Active immunization against hepatitis A in dialysis patients

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Abstract

Background. This study investigated the feasibility, immunogenicity, and reactogenicity of hepatitis A vaccination in end-stage renal failure patients who were on chronic intermittent haemodialysis.

Methods. Forty-three subjects were vaccinated with an inactivated hepatitis A vaccine according to a 0-, 1-, and 6-month immunization schedule. Two groups were established who received the vaccine either intramuscularly (group A, n=30) or subcutaneously (group B, n=13).

Results. All patients in group A and 12/13 in group B developed antibodies against hepatitis A. The geometric mean titres (GMT) were high and similar to those observed in healthy subjects. There was a tendency to higher GMT in the group who received the vaccine subcutaneously. No clinically significant adverse events were observed, and the liver enzyme profile showed no abnormalities.

Conclusions. We showed that hepatitis A vaccination of dialysis patients is feasible, well tolerated and immunogenic and that the vaccine can be given subcutaneously in those patients where intramuscular administration is contra-indicated.

Keywords: dialysis patients; feasibility; hepatitis A; immunization; immunogenicity; reactogenicity

Introduction

Hepatitis A virus (HAV) is transmitted through the faecal–oral route and infection is closely related to standards of hygiene and sanitation. Different clinical patterns have been described with variations reflecting the level of economic development [1]. Infection in children is mostly asymptomatic and hepatitis A is not a clinical problem [2]. With increasing age, HAV infection leads to a more serious disease.

Safe, effective, and highly immunogenic vaccines against hepatitis A have been available for nearly a decade [3–6]. The original vaccine (Havrix™ 720) contained 720 ELISA units (ELU) of hepatitis A antigen and was administered according to a 0-, 1-, 6-month schedule. Since completion of this study, a high-dose formulation has become available (Havrix™ 1440) which is designed as a two-dose vaccine (0, 6–12 month schedule) [7].

Data on hepatitis A vaccination in haemodialysis patients is limited [8,9]. These patients are known to be immunocompromized and are at increased risk of developing severe hepatitis [9]. Haemodialysis patients and especially those with underlying liver disease like chronic hepatitis B or C should be vaccinated against hepatitis A [10,11]. In addition, the travel activity of dialysis patients has increased substantially, facilitated by a worldwide net of holiday dialysis centres, thereby increasing the chances of acquiring a HAV infection. Moreover, the response to the vaccine may be poor or suboptimal and short, due to the dialysis-associated immune defect, and according to the experiences with hepatitis B vaccination [12]. This study therefore investigated the feasibility, immunogenicity, and side effects of hepatitis A vaccination in end-stage renal failure patients.

Subjects and methods

Recruited patients were allocated to two study groups. Haemodialysis patients in group A received the vaccine on dialysis-free days by deep intramuscular injection in the deltoid muscle of the arm opposite to that used for haemodialysis. In patients of group B the vaccine was administered on a haemodialysis day, and was done subcutaneously above the deltoid muscle in the arm opposite to the shunt arm. The vaccination schedule for both groups was 0, 1, and 6 months. The vaccine was Havrix (SmithKline Beecham...
Table 1. Clinical characteristics for all study patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>49 ± 16</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>30/13</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165 ± 27</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61 ± 19</td>
</tr>
<tr>
<td>Years since diagnosis of renal failure</td>
<td>7.6 ± 6.3</td>
</tr>
<tr>
<td>Nephrotic disorder</td>
<td>33%</td>
</tr>
<tr>
<td>Interstitial nephritis (%)</td>
<td>21%</td>
</tr>
<tr>
<td>Diabetic nephropathy (%)</td>
<td>21%</td>
</tr>
<tr>
<td>Nephrosclerosis (%)</td>
<td>9%</td>
</tr>
<tr>
<td>Other (%)</td>
<td>16%</td>
</tr>
<tr>
<td>Years on dialysis</td>
<td>2.8 ± 2.5</td>
</tr>
<tr>
<td>Dialysis/week (h)</td>
<td>12 ± 3</td>
</tr>
<tr>
<td>High-flux membranes (%)</td>
<td>23%</td>
</tr>
<tr>
<td>Erythropoietin therapy (%)</td>
<td>37%</td>
</tr>
<tr>
<td>Erythropoietin/week (i.u.)</td>
<td>3549 ± 2448</td>
</tr>
</tbody>
</table>

Biologics, Rixensart, Belgium) and contained at least 720 ELU inactivated hepatitis A virus from the HML175 strain grown in human MRC5 cells. The vaccine is formulated on aluminium salt and contains 2-phenoxethanol as preservative.

All patients were submitted to a clinical investigation prior to vaccination, and had given their informed consent prior to study entry. Patients had to be more than 16 years of age to be included, be free of any acute illness, and not be participating in any other clinical study. Exclusion criteria were known hypersensitivity to any vaccine component, treatment with immunosuppressive drugs, and administration of blood products during a period of 3 months prior to the study.

Patients were observed closely for 30 min after each vaccination. Patients obtained diary cards to record any local or general adverse event. Blood sample assessments were taken in all patients prior to the first vaccination, 2 weeks after the second vaccination, prior to the third vaccine dose, and finally 2 weeks after the third dose. In order to have a detailed seroconversion profile, blood was taken from a subset of patients prior, 1 and 2 weeks after the first and third immunization. The blood samples were tested by ELISA at the Institute of Virology, University of Cologne, Germany. The assay cut-off was 20 mIU/ml.

To document any liver reactions, serum concentrations of aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), lactate dehydrogenase (LDH), alkaline phosphatase (AP) and gamma glutamyltransferase (GGT) were determined in a subset of 27 patients in the 1st, 2nd, and 3rd week after the first immunization.

Results

A total of 43 patients were enrolled, of whom 30 were included in group A (intramuscular administration) and 13 in group B (subcutaneous administration). In group A, 27 of 30 patients and in group B all patients completed the vaccination schedule.

The main clinical characteristics of the patients enrolled in this study are listed in Table 1. Two patients had type I diabetes mellitus and 16 had type II diabetes mellitus. A total of 19 patients were on antihypertensive medication, 16 were treated for renal anaemia with erythropoietin. All patients had evidence of renal osteopathy. On average, the patients had had 91 ± 76 months of known renal insufficiency and had been on chronic intermittent haemodialysis for 33 ± 30 months.

A total of 11 patients in group A and two patients in group B had pre-existing antibodies to hepatitis A. They were also vaccinated. In group A, 12 of 16 patients seronegative at study entry (75%) had anti-HAV antibodies 1 week after the first vaccination. Two weeks after the first vaccination the response rate was 86% and 2 weeks after the second vaccination all patients had anti-HAV antibodies (100% response). In group B, 10 of 11 (91%) of the initially seronegative patients were seropositive 1 week after the first vaccination, and remained at that level throughout the study.

In group A, in initially seronegative patients, geometric mean titres (GMT) were 759 mIU/ml 2 weeks after the first dose, 268 mIU/ml prior to the second dose, 535 mIU/ml 2 weeks after the second dose, 441 mIU/ml prior to the third dose, and 2221 mIU/ml 2 weeks after the third dose (Figure 1). In group B, in initially seronegative patients, GMT were 2297 mIU/ml 2 weeks after the first dose, 1417 mIU/ml prior to the second dose, 3444 mIU/ml 2 weeks after the second dose, 608 mIU/ml prior to the third dose, and 4497 mIU/ml 2 weeks after the third dose (Figure 1). For those patients who were anti-HAV antibody positive at study entry the GMT were 5294 mIU/ml at study entry, 7840 mIU/ml 2 weeks after the first dose, 8032 mIU/ml just prior to the second dose, 11490 mIU/ml 2 weeks after the second dose, 7743 mIU/ml just prior to the third dose, and 2240 mIU/ml 2 weeks after the third dose.

Within the study, 126 hepatitis A vaccinations were administered. No subject had any local or general symptoms during the first 30 min after vaccination. In group A, 3/85 instances of moderate pain at injection site, 1/85 of local haematoma, and 1/85 cases of small local swelling were reported. One subject developed an intradermal bulla at the injection site 10 days after vaccination.
the second injection, which spontaneously burst 3 days later. One week later, the skin defect was healed with some little scarring. In group B, no local adverse events were reported from a total of 39 injections. One patient developed herpes labialis 14 days after the first dose. The subject did not develop this symptom after the second or third doses. We found no evidence of increased reactogenicity in initially seropositive patients.

Two patients developed a thrombosis of their haemodialysis fistulae during the study. One case was successfully treated by thrombectomy. The second patient suffered from a severe bacterial shunt infection.

Results of the liver enzyme tests are summarized in Table 2. There were no abnormal elevations except for one patient who had slightly elevated enzyme values, which normalized during the study. A second patient had excessively elevated AP levels that turned out to be of bone origin and were due to tertiary hyperparathyroidism.

Discussion

This study investigated the immune response and side-effects of a hepatitis A vaccine in patients with end-stage renal failure. Nearly all patients responded well to the immunization with 100% anti-HAV antibody response in those who received the vaccine intramuscularly and 91% anti-HAV antibodies in those receiving the vaccine subcutaneously. The vaccine was well tolerated with few local symptoms reported by the recipients. This is in accordance with the established safety profile of the hepatitis A vaccine in healthy subjects [13,14].

The seropositivity levels and GMT obtained soon after the first dose and in response to the third dose were found to be within the same range as reported in studies in a healthy population [7,13,15]. These results strongly suggest that the disease status of these patients had not influenced the immune response to the hepatitis A vaccination. This observation is in contrast to the results reported after hepatitis B vaccinations in dialysis patients where antibody formation was found to be significantly impaired compared to healthy subjects [16–19]. However, hepatitis B vaccine is a recombinant subunit vaccine whilst the hepatitis A vaccine used in our study was an inactivated whole virus-based vaccine.

Another factor may be age differences in study populations or the mean time the patients had been on dialysis. Such differences could explain the better immune response to the HAV vaccination. Our results are in line with an observation made with a different hepatitis A vaccine in a study in Japan [9] whereby a better immune response was observed after hepatitis A vaccination compared with hepatitis B vaccination in haemodialysis patients.

We found no evidence for any adverse events linked to the vaccination of patients with pre-existing antibodies to hepatitis A, a feature also seen in another study [15]. Their GMT increased moderately upon vaccination. Screening for anti-HAV antibodies prior to vaccination may therefore not be necessary. Subjects who received the vaccine subcutaneously appear to have developed somewhat higher antibody titres, although this was not statistically significant. More importantly, no local bleeding complications could be found, although the administration occurred on the haemodialysis day. This makes the vaccination schedule easier for patients and physicians. A subcutaneous route of administration is normally recommended for patients with congenital coagulation disorders [20]. In such a study of children with haemophilia, a slightly lower immune response was found in patients with subcutaneous hepatitis A vaccination [21]. Whether or not the route of administration might improve the immune response requires further investigation. However, this study confirms the feasibility of subcutaneous administration of a hepatitis A vaccine if medically needed. Liver enzymes measured after immunization do not suggest any change induced by the hepatitis A vaccine, which reassures its safety, even in patients with renal failure. In patients with chronic liver disease the hepatitis A vaccine was shown to be well tolerated and induced a satisfactory immune response [22]. Similarly, a seroconversion rate of 97% has been found in liver-transplant recipients, whereas only 72% of renal-transplant patients developed anti-HAV antibodies, which was probably due to the higher degree of immune suppression in these patients [23].

In conclusion, vaccination against hepatitis A in end-stage renal failure patients seems to be feasible and well tolerated. Moreover, the immune response to the vaccine appears to be similar to that seen in normal healthy subjects and far better than the reduced immune response to hepatitis B vaccination seen in dialysis patients.

Table 2. Liver enzymes in 27 dialysis patients 3 weeks after hepatitis A vaccination

<table>
<thead>
<tr>
<th>Days</th>
<th>ASAT (SD)</th>
<th>ALAT (SD)</th>
<th>LDH (SD)</th>
<th>AP (SD)</th>
<th>GT (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>7.1 (3.1)</td>
<td>7.3 (2.5)</td>
<td>119 (40)</td>
<td>102 (53)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Day 6</td>
<td>5.9 (1.9)</td>
<td>6.7 (2.4)</td>
<td>132 (53)</td>
<td>113 (63)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Day 13</td>
<td>6.3 (2.3)</td>
<td>7.6 (3.1)</td>
<td>149 (54)</td>
<td>131 (79)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Day 27</td>
<td>5.9 (2.1)</td>
<td>7.4 (2.9)</td>
<td>138 (44)</td>
<td>116 (65)</td>
<td>13 (6)</td>
</tr>
</tbody>
</table>

SD in parentheses. ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; LDH, lactate dehydrogenase; AP, alkaline phosphatase; γGT, gamma glutamyltransferase.

References

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