Response to the hepatitis B virus vaccine in haemodialysis patients: influence of malnutrition and its importance as a risk factor for morbidity and mortality

E. Fernández, M. A. Betriu, R. Gómez and J. Montoliu

Nephrology Service, University Hospital Arnau de Vilanova, Lleida, and Department of Medicine, University of Lleida, Spain

Abstract

Objective. To assess if malnutrition influences the response to the hepatitis B virus vaccine in haemodialysis patients and whether this correlates with morbidity and mortality in these patients.

Design. A 4-year prospective open study.

Setting. Haemodialysis unit of a 434-bed University Hospital.

Patients. Sixty-four patients with end-stage chronic renal failure on maintenance haemodialysis.

Interventions. Three-dose vaccination series with recombinant hepatitis B virus vaccine.

Measurements. Antibody formation against the vaccine, predialysis serum urea, serum albumin and prealbumin, dialysis efficacy (Kt/V), arm muscle circumference, triceps skinfold, serum parathyroid hormone concentration, mortality and morbidity (hospital days per year of dialysis).

Results. Increase in age negatively influences the formation of antibodies ($P = 0.01$), whereas serum albumin ($P = 0.008$) and predialysis blood urea concentration ($P = 0.004$) are positively correlated with the formation of antibodies. Responders had significantly higher levels of serum albumin and prealbumin and predialysis blood urea than non-responders. The percentage of non-responders was higher (70%) in the group with predialysis blood urea concentration between 90 and 125 mg/dl than in those with predialysis blood urea concentration between 176 and 225 mg/dl (14.2%). Patients with serum albumin levels between 3 and 3.5 g/dl were non-responders in a higher percentage (87.5%) than those with serum albumin levels between 4.5 and 5 g/dl (18.8%).

After a 4-year follow-up, survival was 20% higher in the responder group ($P < 0.05$). Morbidity, expressed as hospital days per year of haemodialysis, was markedly lower in the responder group ($10.4 \pm 2$ versus $32 \pm 14$ days, $P = 0.03$).

Conclusions. Malnutrition negatively influences the response to the hepatitis B virus vaccine in haemodialysis patients. Non-responders have higher morbidity and mortality than responders, and therefore the absence of response to the hepatitis B vaccine can be considered as a risk factor in the haemodialysis population.

Key words: malnutrition; hepatitis B virus vaccine; morbidity; mortality; haemodialysis

Introduction

Ample clinical evidence incriminates malnutrition as an important risk factor for morbidity and mortality in haemodialysis patients [1–3]. Extensive epidemiological studies indicate that infection is the second most common cause of death [4,5] in these patients. Moreover the relation between immune competence and nutritional status is well established [6–8].

A lower percentage of haemodialysis patients respond to the hepatitis B virus vaccine (HBVV) than in the normal population [9–14]. The ability to form antibodies in response to this antigenic stimulus requires functional integrity of T and B lymphocytes and macrophages and quite accurately reflects the immune status.

In haemodialysis patients there is a high incidence of malnutrition [3], which can unfavourably influence the immune response, as well as morbidity and mortality. Therefore we evaluated the influence of the nutritional status on the response to the HBVV and determined whether the lack of ability to form antibodies in response to this antigenic stimulus is a risk factor for morbidity and mortality in the haemodialysis population.

Subjects and methods

We studied 64 patients, 48 males and 16 females, aged 17–81 years (average 58 years) who had been on haemodialysis for
whether the ability to form antibodies in response to the hepatitis B virus with an enzyme-linked immunosorbent assay. According to internationally accepted standards [12], those patients with a serum antibody level equal to or higher than 10 mUI/ml were considered immune protected. This group of patients formed the ‘responders’ group and those failing to attain this antibody level were included in the ‘non responder’ group.

In order to evaluate the influence of nutritional status on the response to the HBV, we studied the following parameters:

- Patient demography: age (years), sex, and duration of haemodialysis therapy (months).
- Dialysis efficacy: Urea kinetic model (Kt/V).
- Nutritional status: (a) biochemical data, serum albumin (g/dl) and prealbumin (mg/dl), midweek predialysis serum urea concentration (mg/dl); (b) kinetic data, protein catabolic rate (PCR) (g/kg/day); (c) anthropometric measurements, arm muscle circumference (AMC) (cm) and triceps skinfold (TSF) (mm).

We also measured (i) PTH (pmol/l) since there is experimental evidence supporting an inhibitory effect of parathormone on T and B lymphocytes [15,16].

Kt/V and PCR were measured by the urea kinetic model [17] with the HDS (Hospal, Basel, Switzerland) software, which takes into account residual renal function. Blood samples were taken from a peripheral vein, 10 min after the end of the haemodialysis session to avoid dilution caused by recirculation of the arteriovenous fistula.

Anthropometric measurements were determined only for 31 patients. We calculated the average of three consecutive measurements of the arm contralateral to the fistula site taken immediately after the haemodialysis session. All the measurements were performed by the same nurse and are given in percentiles referred to the normal population of Catalonia [18].

Blood samples for determination of predialysis serum urea, albumin and prealbumin were taken prior to the midweek dialysis session. The values of the biochemical parameters and kinetic calculations included in the statistical study correspond to the average of three determinations at 3-month intervals encompassing the period between the first vaccination and evaluation of the response.

Serum albumin and prealbumin were measured by nephelometry. Intact PTH was measured by immunochromiluminescence (Magic Lite Intact PTH immunoassay, Ciba Corning Diagnostics Corporation, Medfield, MA, USA).

Statistical analysis was performed by multiple logistic regression using the backward stepwise method (Wald), and using the response to the vaccine as the dependent variable. We used Student’s t test for the comparison of the mean values. Software support was provided by SPSS/PC+.

The responder and non-responder groups were analysed separately using the Kaplan–Meier method to evaluate whether the ability to form antibodies in response to the HBV has prognostic value for survival. All patients were included in this analysis and the period of observation was from the first vaccination to a maximal time of 48 months. We used the Mantel–Haenszel test that measures global differences (Serono Data Center Software, Dr J. Almenar Cubell, Valencia) to determine if the difference in survival between the two groups was statistically significant. The results are expressed as means ± SEM.

Morbidity was expressed as hospital days/patients/year of dialysis. In this calculation we censored patients including the first hospitalization from the first hospital day.

Results

Of the 64 patients studied, 39 formed antibodies to the HBV (responders, 60.9%) and 25 did not (non-responders, 39.1%).

Table 1 shows the odds ratio and correlation coefficients of the parameters along with statistical significance. Predialysis serum urea (P = 0.004) and serum albumin (P = 0.008) are correlated positively with the response to the vaccine whereas age is negatively correlated (P = 0.01).

The mean predialysis serum urea in the responder group was significantly higher than in the non-responder group (171.1 ± 5 vs 145.2 ± 5 mg/dl, P < 0.001). (To convert serum urea concentration to blood urea nitrogen concentration multiply by 0.452.)

In order to more precisely evaluate the influence of predialysis serum urea levels on the response to the HBV, we divided the patients into groups according to different ranges of predialysis serum urea and serum prealbumin levels. Table 2 shows the relative risk of failing to respond to the HBV and the degree of statistical significance obtained by Fisher’s exact test when comparing the different groups with the reference one.

Mean age was lower in the responder than in the non-responder group (52.9 ± 2.3 vs 65.3 ± 2.3 years respectively, P < 0.01).

Although the mean PCR value was higher in the responder group, it was not statistically different from the value obtained in non-responders (1.12 ± 0.2 vs 1 ± 0.2 g/kg/day respectively, P = ns).

Mean serum prealbumin levels were significantly higher in the responder than in non-responder group (36.6 ± 0.93 vs 32.06 ± 1.1 mg/dl, P = 0.02).

Table 1. Factors influencing the response to the hepatitis B virus vaccine

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Odds ratio</th>
<th>Correlation coefficient (r)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.10</td>
<td>-0.22</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>0.11</td>
<td>0.24</td>
<td>0.008</td>
</tr>
<tr>
<td>Predialysis serum urea (mg/dl)</td>
<td>0.96</td>
<td>0.26</td>
<td>0.004</td>
</tr>
</tbody>
</table>

This Table shows the parameters selected as statistically significant in the regression analysis using the backward stepwise method, with the response to the vaccine serving as the dependent variable.
Table 2: Relative risk of response failure to HBV in patients divided into groups according to different ranges of serum albumin and predialysis serum urea.

<table>
<thead>
<tr>
<th>Serum albumin (g/dl)</th>
<th>Non-responders (%)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>&lt;3</td>
<td>—</td>
</tr>
<tr>
<td>Group 2</td>
<td>3.01–3.5</td>
<td>87.5***</td>
</tr>
<tr>
<td>Group 3</td>
<td>3.51–4</td>
<td>54.5**</td>
</tr>
<tr>
<td>Group 4</td>
<td>4.01–4.5</td>
<td>31</td>
</tr>
<tr>
<td>Reference group</td>
<td>4.51–5</td>
<td>18.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Predialysis serum urea (mg/dl)</th>
<th>Non-responders (%)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>90–125</td>
<td>70***</td>
</tr>
<tr>
<td>Group 2</td>
<td>126–150</td>
<td>50**</td>
</tr>
<tr>
<td>Group 3</td>
<td>151–175</td>
<td>41.1</td>
</tr>
<tr>
<td>Reference group</td>
<td>176–225</td>
<td>14.2</td>
</tr>
</tbody>
</table>

Fisher's exact test was used to calculate statistical differences and significance between groups. ***P < 0.001, **P < 0.01.

With the exception of four patients Kt/V was higher than 0.90 ranging from 0.76 to 1.6 with an average of 1.1 ± 0.2. This factor was not significantly associated with the response to the HBV, neither were (i)PTH, sex or duration of dialysis therapy.

Survival analysis

Thirty-one patients were vaccinated in April 1989 and observed for 4 years. The remaining patients were vaccinated at the time of admission to the haemodialysis programme and their follow-up period varies widely.

Of the 31 patients followed for 4 years, three in the responder group (7.6%) and seven in the non-responder group (28%) died. Figure 1 shows that the survival difference between both groups is statistically significant.

Morbidity

Mean hospital days per year of haemodialysis were markedly lower in the responder (10.4 ± 2 days/year, range 0–61.6) than in the non-responder group (32.2 ± 14 days/year, range 0–350 days/year). The difference between means was statistically significant (P < 0.03).

Discussion

In our series, the percentage of patients responding to the HBV is 60.9%, which is similar to the results obtained by other groups [4,5,9–11]. This percentage is lower than in the normal population, despite using a double vaccination dose, reflecting the immune deficiency of patients with chronic renal failure [5,9,11]. Antibody formation by B lymphocytes in response to the HBV depends on T-cell stimulation. Therefore the absence of response can be the result of a defect in humoral or cell-mediated immunity, or both. Recent advances have emphasized the important role of macrophages in the release of immune modulators such as interleukin 1, interleukin 2, B-cell stimulation factor 1, interleukin 4, prostaglandins, etc. [19]. In haemodialysis patients, overstimulation of monocytes and lymphocytes induced by the dialyser membrane could alter the production of these mediators and therefore of the immune response [20]. The important clinical manifestations of immune deficiency in patients with chronic renal failure have been the subject of several reports [21–27] showing that the complex immune response is altered at several levels and by different mechanisms. Our goal in this work was to demonstrate the close relationship that exists between immunity and malnutrition in haemodialysis patients, as it has been demonstrated in patients without renal failure [6–8]. This is particularly relevant in the light of recent data [1] which point to serum albumin as the most important prognostic factor for survival in haemodialysis patients, as it has been demonstrated in patients without renal failure [6–8]. It is particularly relevant in the light of recent data [1] which point to serum albumin as the most important prognostic factor for survival in haemodialysis patients, as it has been demonstrated in patients without renal failure [6–8]. This is particularly relevant in the light of recent data [1] which point to serum albumin as the most important prognostic factor for survival in haemodialysis patients, as it has been demonstrated in patients without renal failure [6–8]. This is particularly relevant in the light of recent data [1] which point to serum albumin as the most important prognostic factor for survival in haemodialysis patients, as it has been demonstrated in patients without renal failure [6–8]. This is particularly relevant in the light of recent data [1] which point to serum albumin as the most important prognostic factor for survival in haemodialysis patients, as it has been demonstrated in patients without renal failure [6–8].
this view, in the sense that the higher urea generation during the interdialysis period that comes from protein catabolism is positively correlated with antibody formation.

Serum albumin is a protein synthesized in the liver, and is used clinically to evaluate protein malnutrition. A considerably reduced serum albumin level is a poor prognostic factor, regardless of the primary disease. In our patients, hypoalbuminaemia negatively influences the response to HBVV. It is of note that even minimal variations within the normal range cause noticeable changes in the percentage of patients responding to this antigenic stimulus. This observation confirms the data published in the multicentre studies on mortality risk in haemodialysis patients [1,2], where patients with serum albumin levels between 3.5 and 4 g/dl (within the normal range) have a relative risk of death twice that of patients with serum albumin levels over 4 g/dl. These data raise the question of defining what are adequate serum albumin levels in haemodialysis patients.

Non-responders had a lower survival rate and therefore a poorer prognosis. Moreover, morbidity measured essentially as hospital days per year of haemodialysis was also higher in non-responders, suggesting that the immune deficit is responsible for many of the complications of haemodialysis patients. Our results suggest that the immune deficit is one of the effector pathways through which malnutrition increases the risk of morbidity and mortality in haemodialysis patients. It is clear that malnutrition and poor immune response are interrelated, but other factors can also influence immune responsiveness in dialysis patients.

In vitro studies have demonstrated an inhibitory effect of PTH on T and B lymphocytes [19,20]. In our patients we did not observe an association between PTH levels and response to the HBVV, but the situation in vivo can be different from experimental conditions. Experimentally, acute PTH loads were administered, whereas patients with chronic renal failure have sustained PTH elevations.

To summarize, our results indicate that malnutrition unfavourably influences the response to the HBVV in haemodialysis patients. Serum albumin and predialysis serum urea concentrations are the strongest predictors of response to the HBVV. Since minimal changes in serum albumin induce significant changes in the immune response, its level should be closely followed in haemodialysis patients. Our results also demonstrate that the absence of response to HBVV can be considered as a risk factor for morbidity and mortality in the haemodialysis population. It is therefore necessary to identify high-risk patients and start appropriate actions to correct malnutrition in order to avoid subsequent complications.

Acknowledgements. This work has received the grants SM-90-0003 and SM-91-0024 from DGICYT (Ministry of Education and Science of Spain).

References

Malnutrition and response to the hepatitis B virus vaccine in haemodialysis


Received for publication: 28.9.95
Accepted in revised form: 2.4.96