The Effect of L-carnitine on Lipid Metabolism in Patients on Chronic Haemodialysis

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Abstract. Twenty-one patients (median 49 years; range 20–72 years) on chronic haemodialysis (median: 54 months; range 16–154 months) were examined in a clinical controlled trial for the effect of carnitine on hyperlipoproteinaemia. Initial values of serum carnitine were within the normal range. Carnitine was added to the dialysis fluid to a final concentration of 100 μmol/l. The trial was carried out for 6 months, and the serum of fasting patients was analysed at monthly intervals for carnitine, triglycerides, HDL-cholesterol, LDL-cholesterol and apolipoprotein A and B. The loss of carnitine to the dialysis fluid also was examined, as was the retained amount in those receiving carnitine. We could not confirm the findings of others [1,2,3,4,5] that carnitine produces lowering of serum triglycerides and increases of serum HDL-cholesterol.

The study was extended for another year with ten patients; however, no change was observed in the lipid pattern.

Key words: Carnitine; Haemodialysis; Lipid metabolism

Introduction

Patients on chronic haemodialysis show variable disturbances in the metabolic turnover of fatty acids, triglycerides, and lipoproteins [6,7,8]. Characteristically one finds type IV hyperlipoproteinaemia manifest by increased serum triglycerides. Furthermore, there is often a lowering of serum HDL-cholesterol [8,9]. These factors probably contribute to the development of premature cardiovascular disease seen in patients on long-term haemodialysis [10].

It has been shown that in some instances these patients present with an abnormally low content of the amino acid carnitine in their serum and skeletal muscle [11,12]. This is taken to support the hypothesis that lack of carnitine, a cofactor in the intramitochondrial oxidation of long-chain fatty acids, is involved in the metabolic disturbance of fatty acid oxidation resulting in increased serum triglycerides and decreased serum HDL-cholesterol in haemodialysis patients.

Treatment with carnitine has been reported to be accompanied by a reduction in serum triglycerides [1,2,3], although serum carnitine was found to be normal or supernormal. Also, an increase in serum HDL-cholesterol has been demonstrated [4,5]. In these previous studies, carnitine had been administered almost exclusively orally or intravenously to ensure a sufficient uptake by the patient. In a single trial [13] carnitine had been added to the dialysis fluid.

Different dialysis procedures (i.e. dialysis time, membrane construction etc.) make it difficult to compare results obtained by treatment with carnitine administered orally or intravenously with studies in which carnitine was added to the dialysis fluid. We present results from a recirculating system to which carnitine was added for 6 months to the dialysis fluid.

Materials and Methods

Thirty-seven patients (27 males and 10 females) who had been on haemodialysis for at least 6 months (3–4 h thrice weekly) gave informed consent to take part in the trial. Ten
L-carnitine and Lipid Metabolism in Chronic Haemodialysis

Table 1. Data for the placebo and carnitine group respectively, at start and after 6 months of therapy

<table>
<thead>
<tr>
<th>Serum substances measured</th>
<th>Start values</th>
<th>Final values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Carnitine</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.6 ± 1.3</td>
<td>2.7 ± 0.7</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.2 ± 1.8</td>
<td>4.9 ± 1.1</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>0.7 ± 0.1</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>3.4 ± 1.5</td>
<td>3.0 ± 1.0</td>
</tr>
<tr>
<td>Apolipoprotein A (g/l)</td>
<td>1.5 ± 0.3</td>
<td>1.5 ± 0.3</td>
</tr>
<tr>
<td>Apolipoprotein B (g/l)</td>
<td>1.1 ± 0.3</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>*Carnitine (μmol/l)</td>
<td>61.9 ± 11.0</td>
<td>62.0 ± 10.9</td>
</tr>
</tbody>
</table>

Only values for *serum carnitine in the group treated with carnitine were significantly changed during the period. All values are mean ± 1 SD. NS = not significant

Results

Table 1 summarises the results. As shown, there was a significant (P < 0.001) increase in serum carnitine (normal values ± 2 SD: 52.1 ± 20.4 μmol/l [14]) after 6 months of treatment. This elevation of serum carnitine did not, however, promote any decrease in serum triglycerides. In one patient serum triglycerides decreased from 4.0 mmol/l to 0.7 mmol/l and remained at a low level throughout the trial, but this tendency was not confirmed in the group as a whole. The serum values for HDL-cholesterol did not show any change in either group during the 6 months, and neither did cholesterol or LDL-cholesterol. The serum content of apolipoprotein A and B also remained unchanged comparing the carnitine-treated group to the placebo group.

To evaluate the possible influence on serum carnitine by our closed system compared with open system, we measured serum carnitine in 11 patients on chronic haemodialysis for at least 6 months using an open dialysis fluid system (Gambro AK 10). We did not find any difference in serum carnitine (median, 63; range, 51–93 μmol/l) compared to those in our series.

There was no correlation between the value for serum carnitine and the period during which haemodialysis was performed (r = -0.1717; P > 0.4).
Sixteen patients were treated with either beta-blocking agents (n = 11) and/or diuretics (n = 5). There was no significant difference in the distribution of these treatments among the two groups.

The loss of carnitine to the dialysis fluid is seen in Table 2. There was a significant correlation between the total loss of carnitine and the number of consols used (r = 0.7766; P < 0.001). Those patients treated with carnitine retained this in the amounts shown in Table 3.

**Table 2. Amount of carnitine lost during dialysis in the placebo-treated group**

<table>
<thead>
<tr>
<th>Loss of carnitine</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 consol (n = 5)</td>
<td>218</td>
<td>68-435</td>
</tr>
<tr>
<td>2 consols (n = 4)</td>
<td>446</td>
<td>217-525</td>
</tr>
<tr>
<td>3 consols (n = 1)</td>
<td>870</td>
<td>555-1440</td>
</tr>
</tbody>
</table>

Values in μmol/dialysis

**Table 3. Retained amount of carnitine in the carnitine-treated group**

<table>
<thead>
<tr>
<th>Retained amount of carnitine</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 consol (n = 7)</td>
<td>3750</td>
<td>1350-5625</td>
</tr>
<tr>
<td>2 consols (n = 4)</td>
<td>6450</td>
<td>5175-8700</td>
</tr>
</tbody>
</table>

Values in μmol/dialysis

Finally, among the patients included in the trial, there was no significant correlation between the four variables: serum LDL-cholesterol, serum HDL-cholesterol, serum triglycerides or serum cholesterol, and the value for serum-creatinine.

**Discussion**

Since Boehmer et al. [11] described carnitine deficiency in patients on chronic haemodialysis, clinical trials have been carried out to achieve a quantitative and qualitative expression of the metabolic effect of this deficiency. Also, a number of cases referred to as primary carnitine deficiencies have been evaluated [15,16]. These conditions often show dramatic improvement in response to oral carnitine treatment [17,18]. However, these primary carnitine deficiencies seem to be extremely rare, at least in comparison to those deficiencies induced by haemodialysis.

The pathogenesis of secondary carnitine deficiency in haemodialysis patients is poorly understood. Normal or even supernormal concentrations of carnitine are often found in serum [1,19,20]. Most patients, however, show reduced amounts of carnitine in skeletal muscle tissue [3,11,21,22], which is the principal depot for carnitine [23]. The amount of carnitine needed to keep serum values in the normal range is only a tiny fraction of the amount available from muscle tissue. Therefore, even subnormal amounts in skeletal muscle are sufficient to maintain normal serum concentration by dynamic exchange.

Over extended periods of haemodialysis treatment the muscle depots are diminished [11] to such an extent that the serum content is difficult to maintain at a normal level. At this point lipid metabolism may be disturbed. Whether uraemia per se or carnitine deficiency is the main cause of this disturbance of metabolism is not easily demonstrated. Carnitine therapy has been shown [1,2,4,5,24] to return the serum levels of triglycerides and HDL-cholesterol to normal. In contrast to this there is some evidence for a lack of effect from carnitine treatment [25] or even amelioration of serum triglycerides [26].

In most cases carnitine has been administered by the oral or intravenous routes. The reasons behind supplementing carnitine by the dialysis fluid are two: first is the aim of diminishing the loss during dialysis due to diffusion caused by a concentration gradient, thus avoiding the need for oral supplementation; second, adding carnitine to the dialysis fluid minimises or prevents fluctuations in serum carnitine during dialysis. Bizzi et al. [13] have, in short-term dialysis, shown that addition of carnitine to the dialysis fluid prevents reduction of serum carnitine during the dialysis procedure.

The effect of dialysis-fluid-supplemented carnitine on the lipid pattern has not been adequately elucidated. Our endeavours did not result in any significant effect on the serum content of triglycerides and HDL-cholesterol, even though we noted a clearly defined increase in serum carnitine during the treatment period. The extension of the treatment for a further year with a residual number of ten patients, and a doubling of the carnitine content of the fluid, did not bring about any further change.

Alternatively, the route of administration (i.e. by way of the dialysis fluid) could be physiologically improper. This, as mentioned, seems unlikely in as much as the serum carnitine was raised significantly.

Discrepancies concerning the influence of the haemodialysis procedure on fat metabolism may be explained in several ways. The frequency and length of each dialysis for earlier works varies, or is unknown [3,4,5]. The total period of dialysis, however, should be considered of particular importance, although we did not find any correlation between the lipid variables and serum creatinine. Some workers have not reported these data [2,4,5], and in others [1,3] it varies. Also to be considered is the presence or absence of glucose in the dialysis fluid. The patients presented here were treated with fluid containing no glucose, whereas other investigators have used glucose-enriched fluid in their schedule [1]. In some studies [3,5,26] these data are not presented. Bougneres et al. [2], using no glucose in the dialysis fluid, showed a hypolipaemic effect of carnitine.
Furthermore, dietary habits may differ considerably between the north and south of Europe.

In conclusion, from a Danish study of patients treated by chronic haemodialysis for more than 6 months (single-pass and recirculating systems), no reduction in serum carnitine could be found. About 50% of patients treated with recirculating systems [21 of 37] exhibited abnormalities in fat metabolism confined to a type IV hyperlipoproteinaemia. Carnitine added to the dialysis fluid did not promote any changes in the lipid pattern in spite of a significant increase in serum carnitine.

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References