Introduction

One third of all diabetic patient are affected by peripheral diabetic neuropathy (PDN) (1). Prevalence of PDN varies from 15% to 50% according to the age of patients and duration of illness (1, 2). The measurement of the P300 event-related potential (ERPs) latency is an indicator of the psychomotor performance (3). It reflects the attention and short term memory (4, 5). There are some studies, which show P300 latency alteration on the diabetic patients (6, 8).

In the treatment of diabetic neuropathy many different treatment protocols or medicines are used or tested. Gamma linolenic acid (GLA), which is an essential fatty acid, is an important precursor of prostaglandins. There is a disorder in the transforming of the linolenic acid to GLA and further to dihomo-GLA and arachidonic acid. These components are important structural components of neuronal membranes phospholipids (9).

It is known that l-carnitine diminishes in the sciatic nerve of diabetic patients (10). Treatment with acetyl-l-carnitine (ALCAR) normalises the level of the enoneural l-carnitine. It decreases the activity of the polyol, which is high on the diabetes, and regulates nerve conduction disorders by decreasing the synthesis and axonal transport of the substance P (11, 12). ALCAR also has a free radical scavenging effect (13).

In GLA group, peroneal nerve motor conduction increased by 2.3%, sural nerve sensory conduction increased by 4.1%, P300 latency decreased by 0.7%, in the GLA+ALCAR group these results were 6.4%, 8.3% and 1.6% respectively.

These findings suggest that GLA is an effective and safe agent in PDN and in the complications of diabetes on the central nerve system, and the combination of GLA with ALCAR is increasing this effectiveness.

Key words: Acetyl l-carnitine, peripheral diabetic neuropathy, gamma linolenic acid, P300 latency
Patients and Methods

This study includes sixty NIDDM patients, whose peroneal and sural nerve conduction velocity was low according to the norms of our electrophysiology laboratory. Fifteen patients were excluded from the study either due to side effects of medicines or for some other reasons, explained in the “results” part of this paper, so the treatment was concluded with 45 patients. Twenty-six patients were male and 19 were female. Average age was 55±5 in the GLA group (group 1) and 56±5 in the GLA+ALCAR group (group 2). The duration of illness was 2.3±1.8 years for group 1 and 3.6±2.1 for group 2. The average HbA1c level was 7.5±4.1% and 7.3±3.9% respectively for both group. The treatment was formed from oral antidiabetics and diet. According to mini mental examination dementia patients with depression according to the Hamilton depression scale, with a systemic illness, chronic alcoholism or hearing impairment were not included in the treatment. 360 mg/day GLA were given to 24 patients in the first group and 360 mg/day GLA and 1gr ALCAR were given to 21 patients in the second group during a 6 month period. Before and after treatment, the velocity of peroneal nerve motor and sural nerve sensory were calculated for both groups. For the peroneal nerve if the velocity between fibular head and wrist among is less than 41.65 m/s, or for the sural nerve if the velocity between lateral malleolus and mid-calf is less than 35 m/s, sensory response measurement from peak, were accepted as PDN.

A dantec Keypoint Electrodiagnostic system was used for nerve conduction studies and ERPs records. To obtain ERPs, the conventional technique with an acoustic odd-ball paradigm was used. Dantec silver/silver chloride surface electrodes were used for all records. Records were calculated from Fz, Cz, and Pz. Bandwidth filters were 0.2-30 Hz. Standart signal was 1 kHz, target sounds were 2 kHz, 15% odd-ball, randomised stimulation frequencies were minimum 0.3 Hz and maximum 1.0 Hz. Stimulus intensity was 70 dB above hearing level. Test patients pressed the button held near their dominant hands upon hearing each target sound. P300 wave was accepted as the widest positive point after negative-positive-negative (N1-P2-N2) resultant values. The patients were called for monthly controls. The patients, whose HbA1c values were more than 50% of the basic value, were excluded.

Statistical Analysis: Analysis was presented with SPSS 7.5 for Windows program. The results of the groups before and after treatment were compared in two different paired series. The percentage values of the groups were compared using student t test. P<0.05 was accepted statistically significant (two-tailed).

Results

P300 latency and peripheral nerve conduction of the 24 NIDDM patients, who were treated with GLA, showed statistically significant improvement compared with pre-treatment levels. Findings are shown in Table 1.

Table 1. Nerve conduction and P300 latency values of group (GLA) are before and after treatment (n:24).

<table>
<thead>
<tr>
<th>Tests</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroneal motor</td>
<td>42.05±4.92 m/s</td>
<td>42.98±4.72 m/s</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sural sensitive</td>
<td>31.54±1.84 m/s</td>
<td>32.81±1.71 m/s</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P300</td>
<td>346.79±15.0 m/s</td>
<td>344.16±14.94m/s</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 1. Twenty-one patients given GLA+ALCAR treatment showed a significant recovery. Findings are shown in Table 2.

Table 2. Nerve conduction and P300 latency values of group 2 (GLA+ALCAR) are before and after treatment (n:21).

<table>
<thead>
<tr>
<th>Tests</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroneal motor</td>
<td>39.56±3.92 m/s</td>
<td>42.10±4.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sural sensitive</td>
<td>30.20±2.15</td>
<td>32.75±3.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P300</td>
<td>346.95±14.35</td>
<td>341.04±11.91</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2. The recovery in the electrophysiological findings of the patients treated with GLA+ALCAR in group 2 was more significant compared with the patients treated with GLA in group 1 (p<0.001). Statistical information and average values of the findings are summarised in Table 3.

Table 3. Respons to treatments of both of two groups comparative values.

<table>
<thead>
<tr>
<th></th>
<th>4Group 1 n:24 (GLA)</th>
<th>Group 2 n:21 (GLA+ALCAR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroneal motor m/sn</td>
<td>% 2.3±1.5</td>
<td>%6.4±3.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Sural sensitive m/sn</td>
<td>%4.10±2.25</td>
<td>8.3±5.1</td>
<td>0.001</td>
</tr>
<tr>
<td>P300 m/sn</td>
<td>%0.75±0.65</td>
<td>%1.6±1.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Average age (year)</td>
<td>55±5</td>
<td>56±5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Duration of diabetes (year)</td>
<td>2.3±1.8</td>
<td>3.6±2.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>7.5±4.1</td>
<td>7.3±3.9</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>
Table 3. Sural nerve sensory conduction improvement was greater than that of peroneal motor nerve conduction in the both treatment groups.

**Side Effect and Seperation from Study:** Three of thirty patients (10 %) who started with the GLA treatment left the treatment due to side effect. Nausea and headache were the most evident side effects. Two patients were taken out from study due to significant change in the HbA1c percent. One patient had to leave the treatment due to surgical operation. Seven of thirty patients (23 %) who started with GLA+ALCAR treatment left the treatment due to side effects. The patients complained mostly from nausea, vomiting, stomachache and body odour. One patient had to leave the treatment due to a stroke, in addition to another patient with significant change in the HbA1c percent.

**Discussion**

GLA has been used both on animals and people and positive results have been obtained. Jamal et al (14) and three years later Keen et al (15) tested GLA on PDN patients and obtained positive results. However new forms of GLA or using GLA with different components were found out to be more effective according to tests performed on animals. Cameron et al (16) founded out that using ascorbyl gamma linolenic acid in the PDN on rats was much more effective than using GLA alone. Cameron founded out in another study that (17) using a combination of GLA with alpha-lipoic acid was more effective. We tried to combine the GLA with ALCAR to increase the effectiveness too. In our study, while the nerve conduction of the group treated by GLA accelerated by 1-1.5 m/sn, P300 latency decreased by 2.5 sn. While the nerve conduction accelerated by 2.5 m/sn in the group treated by the GLA+ALCAR, P300 latency decreased by 6sn. These results show that GLA and ALCAR had a synergic effect on the PDN.

The alterations of P300 latency in diabetic patients are well known (6, 8). However pathophysiological mechanism of the diabetic central nerve involvement is still undetermined. A connection between peripheral neuroathy and P300 latency has not been found. Even though the effect of the hypoglycemia on the P300 latency is known (18, 19), hypoglycemic episodes was not observed in any of our patients. Considering that cerebrovascular ischemia are often seen in diabetic patients, the alteration of the P300 could be due to this (20). However no history or examination findings indicating stroke were in our patients. The alterations of P300 latency on the dementia and depression are known (21, 22). However, there was no dementia or depression in any of our patients. At present, disorders of the neurotransmitters functions or transition disorders of neurotransmitters at the blood-brain barrier constitute the most valid theory regarding the consciousional impairments in diabetes and hence the reason for the alteration of the P300 latency (23).

The correction of the electrophysiological parameters was limited in our studies. However having considered the intensity of the PDN connected with duration of the diabetes and the nerve fibre lost in the advanced neuropathies (18, 24), this limited recovery could be regarded as natural.

Although the pathophysiology of the P300 latency alteration and reason for the recovery by treatment are not known, GLA treatment produced a significant recovery in the P300 latency and combination with ALCAR enhanced the positive effect. Furthermore this treatment correct also the peripheral nerve conduction partially. An important number of the patients tolerated the side effects of the treatment. Using GLA alone or with ALCAR, seems an effective alternative especially in the early stage of PDN.

**References**


