Peripheral nerve functions in chronic alcoholic patients on disulfiram: a six month follow up

Sarala K Palliyath, Barry D Schwartz, Linda Gant

Abstract

The peripheral nerve functions of chronic alcoholic patients were studied clinically and electrophysiologically before they were placed on disulfiram (Antabuse). The evaluations were repeated while they were treated with 250 mg (n = 33) and 125 mg (n = 9) of disulfiram for one, three and six months. The data were compared with that of 24 untreated chronic alcoholic patients. None of the patients developed overt symptoms of peripheral neuropathy during the period of study. The patients on 250 mg disulfiram showed a significant decline in several components of the peripheral nerve functions, but no significant electrophysiological abnormalities were noted in patients taking 125 mg of disulfiram. Interestingly, the control group showed a significant electrophysiological improvement during the same period of observation.

Disulfiram (Antabuse) has been widely used in the rehabilitation of chronic alcoholic patients for more than forty years. Although peripheral neuropathy (PN) as a complication of disulfiram had been mentioned by Child et al in 1951, the first established case report of disulfiram neuropathy was described by Charatan in 1953. Awareness of this toxicity of disulfiram to peripheral nerves has resulted lately in a surge of anecdotal reports of disulfiram neuropathy. However, most of these reported patients were not evaluated for asymptomatic alcoholic neuropathy before treatment with disulfiram. In addition, some of these patients had well-documented alcohol disulfiram reaction, diagnosis of cirrhosis of the liver and some were on concomitant neuroleptics. Hence, it is difficult to establish the extent of the direct effect of disulfiram on peripheral nerves in these patients. In experimental conditions, however, a toxic neuropathy has been shown to occur in rats while on 250 mg of disulfiram. In a previous pilot study on 15 chronic alcoholic patients treated with 250 mg of disulfiram for three months we noted asymptomatic decline in peripheral nerve functions. The present report is an extension of our previous study on a new group of chronic alcoholic patients on disulfiram and with a matched control group of voluntarily abstinent chronic alcoholic patients without drug therapy. They were studied for six months.

Patients and methods

The control group and the disulfiram group were selected from the alcohol rehabilitation unit. The patients were interviewed within the first week of admission to explain the details of the study. Those who were willing to participate as either controls or as treatment group were asked to sign a consent. The choice of participation in the treatment group was voluntary; however, occasionally it was partly influenced by the primary care physician. Thus it was difficult to recruit an equal number of controls, as most of the patients preferred to take disulfiram to maintain abstinence. A very strict selection criteria was followed. Clinical and appropriate laboratory evaluations were done to exclude those who had diseases which can potentially cause peripheral neuropathy, that is, diabetes mellitus, malnutrition, collagen vascular diseases, liver diseases and systemic malignancy. Drug abuse, non-compliance and disulfiram treatment in the past were also considered as exclusion criteria. Eighty-five patients on disulfiram and 35 controls entered the study. Both groups were interviewed by the dietician for the details of nutritional status and alcohol intake. Nutritional status of the patients was classified as good, adequate or poor based on the daily caloric consumption, protein, carbohydrate, fat intake and vitamin supplements, according to protocol. The total duration and quantity (grams/day) of alcohol consumption were also noted. Clinical examination was carried out by the principal author (SP) with special emphasis placed on the peripheral nervous system. Motor strength was documented according to MRC scales; muscle stretch reflexes were recorded as hyperactive, normal, hypactive or absent. Sensory testing of light touch and pain was carried out by conventional methods and recorded as normal, impaired, absent or hyperactive. Vibration sensation was measured at the big toe at the metatarsal bone and the thumb at the metacarpal bone using a Biothesiometer (Bio-Medical Instruments Company, Newbury, Ohio, USA) producing a 100–120 Hz sine wave vibration. Voltage applied at vibration threshold was measured from the voltmeter on a Biothesiometer by the method of limit converted to the amplitude and expressed as microns as described by Goldberg and Lindblom.

Electrophysiological studies

Nerve conduction studies were carried out based on standard techniques. Skin tem-
Table 1  Details of age and nutritional status of all the groups (SE)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age  (Yrs)</th>
<th>Weight (Lbs)</th>
<th>Total calories*</th>
<th>Protein (Grams)†</th>
<th>B vitamin†</th>
<th>Duration of drinking (yrs)</th>
<th>Average daily intake (grams/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>46 (10)</td>
<td>163 (27)</td>
<td>1850 (450)</td>
<td>64 (8)</td>
<td>A</td>
<td>26 (10)</td>
<td>207 (25)</td>
</tr>
<tr>
<td>Disulfiram 250 mg</td>
<td>42 (9)</td>
<td>169 (25)</td>
<td>1925 (495)</td>
<td>58 (10)</td>
<td>A</td>
<td>22 (9)</td>
<td>219 (26)</td>
</tr>
<tr>
<td>Disulfiram 125 mg</td>
<td>40 (10)</td>
<td>159 (21)</td>
<td>1790 (500)</td>
<td>60 (12)</td>
<td>A</td>
<td>23 (9)</td>
<td>230 (18)</td>
</tr>
</tbody>
</table>

*Calories > 1800 Good 1800-1500 Average <1500 Poor

†B Vitamins Good (G) > 2 servings from meat group and 4 servings from grain group.

Electrophysiological studies

The data were analysed by a repeated measures analysis of variance with groups and months of observation as the independent variables. The dependent measures were: (1) distal latency (median and peroneal); (2) motor nerve conduction velocity (median and peroneal); (3) sensory nerve conduction velocity (median and sural); (4) amplitude of compound muscle and nerve action potentials; (5) duration of sensory nerve action potentials. All analyses were performed using a Greenhouse-Geisser (1959) post hoc test.

Results

Clinical

Baseline clinical evaluation of the groups did not differ significantly (table 1). No overt symptoms of peripheral neuropathy were evident in any subjects. Absent ankle-jerk was recorded in two subjects in the control group and three in the disulfiram group. Normal muscle strength and touch and pain sensation were noted in all subjects. Nine out of 42 subjects in the disulfiram group, took only 125 mg of disulfiram daily because of reported drowsiness with 250 mg whereas, the other 33 were on 250 mg per day. These two groups were analysed separately.

None of the subjects developed any acute or subacute symptoms of peripheral neuropathy during the six month study period. There was no change in either muscle strength and reflexes, or touch and pain sensation. The data for vibration perception were analysed by repeated measure analyses of variance. No significant initial differences were observed between the three groups. However, there were statistically significant differences at the third and sixth months of observation between groups (table 2). Interestingly, there was a significant improvement within the control group itself between the first and the last observation period (p < 0.001).

Electrophysiological studies

The data were analysed by a repeated measures analysis of variance with groups and months of observation as the independent variables. The dependent measures were: (1) distal latency (median and peroneal); (2) motor nerve conduction velocity (median and peroneal); (3) sensory nerve conduction velocity (median and sural); (4) amplitude of compound muscle and nerve action potentials; (5) duration of sensory nerve action potentials. All analyses were performed using a Greenhouse-Geisser (1959) post hoc test.

Figure 1  Change in median motor conduction velocity over months. * = P < 0.05 component change within group over 6 months of observation. A = P < 0.05 250 mg disulfiram versus control.
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Figure 2 Change in peroneal conduction velocity over months. * = \( P < 0.01 \) component change within group over six months of observation. A = \( P < 0.05 \) 250 mg disulfiram versus control.

(\( \text{m/s} \))

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Control</th>
<th>Antabuse 125 mg</th>
<th>Antabuse 250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>42</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>1</td>
<td>42</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>44</td>
<td>46</td>
</tr>
</tbody>
</table>

Figure 3 Change in median sensory conduction velocity over months. * = \( \bar{P} < 0.01 \) component change within group over six months of observation. A = \( P < 0.01 \) 250 mg disulfiram versus control.

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Control</th>
<th>Antabuse 125 mg</th>
<th>Antabuse 250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>38</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>1</td>
<td>38</td>
<td>40</td>
<td>42</td>
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<tr>
<td>2</td>
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<td>40</td>
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<td>3</td>
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</tr>
<tr>
<td>6</td>
<td>38</td>
<td>40</td>
<td>42</td>
</tr>
</tbody>
</table>

Discussion

Our data show that there is either no change or a gradual decline in peripheral nerve functions in chronic alcoholic patients when treated with disulfiram. This decline is most likely due to a direct effect of disulfiram as these patients were abstinent throughout the study period and had no other predisposing factors for peripheral neuropathy. Also, our controls were observed on several components to reverse or improve. Though statistically significant difference in conduction velocities was seen at six months when compared to the baseline values, a trend in decline of conduction velocity was obvious by three months. This agrees with our previous findings on 15 chronic alcoholic patients on 250 mg of disulfiram.18

In our experience, the dosage of disulfiram appears to have a role in the degree of peripheral nerve dysfunction. The subjects on 125 mg of disulfiram showed no change in the nerve conduction parameters from baseline through to the end of the study. The case of disulfiram neuropathy reported by Worner21 showed that peripheral neuropathy improved despite continuing disulfiram at a lower dose of 125 mg. It has been suggested that the dose of disulfiram should not exceed 200 mg daily.11 Feldman12 treated his patients with 125 mg and none developed peripheral neuropathy after

Table 3 Mean polyphasic motor units (percentage)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>First month</th>
<th>Third month</th>
<th>Sixth month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>20-22</td>
<td>24-54</td>
<td>18-88</td>
<td>16-77</td>
</tr>
<tr>
<td>Disulfiram 250 mg</td>
<td>23-33</td>
<td>14-44 B</td>
<td>18-33 B</td>
<td>16-66 B</td>
</tr>
<tr>
<td>Disulfiram 125 mg</td>
<td>18-33 B</td>
<td>18-93 A</td>
<td>16-44 B</td>
<td>16-66 B</td>
</tr>
</tbody>
</table>

A = \( P < 0.05 \) 250 mg Disulfiram vs control.
B = \( P < 0.05 \) 125 mg Disulfiram vs control.
* = \( p < 0.05 \) increase in polyphasic motor units cell mean over six months.
continuous use for two years. All the cases of disulfiram neuropathy reported in the literature were on 250 mg or higher. Fulminant polyneuritis after an overdose of disulfiram and alcohol has also been reported.\textsuperscript{15} Thus, we believe that disulfiram at a dose of 125 mg or lower may be a safer level to use.

During a six month period none of our experimental group developed any acute or subacute symptoms of peripheral neuropathy. This contrasts with several case reports in the literature. Most of the patients developed the symptoms within two to three months of disulfiram treatment.\textsuperscript{1,9,12,13} In some cases, treatment with higher doses, alcohol disulfiram reaction, concomitant use of other drugs and a pre-existing alcohol/nutritional neuropathy appear to have contributed to earlier and acute symptoms of neuropathy.\textsuperscript{10,11,14,16} Possibly, the strict inclusion criteria used in this study is associated with the failure to observe symptoms of peripheral neuropathy. Consequently, a thorough neurological examination with emphasis on peripheral nervous system, serial electrodiagnostic studies and a close follow up evaluation would assist in the reduction of disulfiram induced neuropathy.

An interesting finding of this study is the gradual improvement in the peripheral nerve function of the electrophysiological parameters in the control group, (that is, alcoholics abstaining without disulfiram). The needle electromyography study showed a significant increase (p < 0.01) in the amount of polyphasic motor units suggesting an ongoing electrophysiological improvement at the intramuscular nerve level. This observation needs further study to determine the natural course of alcoholic peripheral neuropathy, as the literature on this is scanty. Hillbom and Wennberg\textsuperscript{22} reported seven of ten patients with alcoholic neuropathy showing improvement when re-examined after three to five years. But 11 patients of Hawley, et al.\textsuperscript{24} had no electrophysiological improvement in six months.

Our study shows that there is a clear subclinical decline in peripheral nerve functions within six months of disulfiram treatment with 250 mg daily. Since no significant changes occur with 125 mg it seems logical to treat chronic alcoholic patients with 125 mg disulfiram when necessary, to reduce the toxic effect on peripheral nerves.

We thank Dr DM Gallant and his staff in the Alcohol Rehabilitation Unit for their cooperation, B Moore and R Bauman for technical help, Dr S Ganji for reviewing the manuscript, K Soule and T Andrus for secretarial help and those patients who participated in this study.

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