BENFOTIAMINE IN TREATMENT OF ALCOHOLIC POLYNEUROPATHY: AN 8-WEEK RANDOMIZED CONTROLLED STUDY (BAP I STUDY)

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Abstract — A three-armed, randomized, multicentre, placebo-controlled double-blind study was used to examine the efficacy of benfotiamine vs a combination containing benfotiamine and vitamins B6 and B12 in out-patients with severe symptoms of alcoholic polyneuropathy (Benfotiamine in treatment of Alcoholic Polyneuropathy, BAP I). The study period was 8 weeks and 84 patients fulfilled all the prerequisite criteria and completed the study as planned. Benfotiamine led to significant improvement of alcoholic polyneuropathy. Vibration perception (measured at the tip of the great toe) significantly improved in the course of the study, as did motor function, and the overall score reflecting the entire range of symptoms of alcoholic polyneuropathy. A tendency toward improvement was evident for pain and co-ordination, no therapy-specific adverse effects were seen.

INTRODUCTION

Alcoholic polyneuropathy is a disorder of the peripheral nerves that interferes with sensory, motor, and autonomic nerve function. Whereas mild and moderate forms of the condition cause mainly pain and dysesthesia, severe forms may involve paralysis. Progression of the disorder can cause inability to walk.

About 20% of chronic alcoholics experience axonal degeneration and demyelination of peripheral nerves in the course of their addiction (Heimann and Naumann, 1981); at the same time, their levels of vitamin B1 are significantly lowered (Meyer, 1981). This is due to the nutritional inadequacy of the chronic alcoholic’s diet, which is heavy in carbohydrates. In addition to the deficient supply of thiamine, absorption by the gut is impaired by chronic alcoholism. Furthermore, ethanol reduces the storage capacity of the liver for thiamine, which is low to start with, and additionally the toxic effects of alcohol and its metabolite acetaldehyde interfere with the utilization of vitamin B1 (Bitsch and Bitsch, 1987).

Apart from the requirement of alcohol abstinence, a causal treatment for alcoholic polyneuropathy is long-term administration of vitamin B1. Effective oral treatment with vitamin B1 requires high bioavailability of the active principle. However, intestinal absorption of water-soluble thiamine depends on active saturation transport, so that, even in healthy persons, the rate of absorption of therapeutic doses (50–100 mg) is relatively small (4–6%) (Heinrich, 1990). In alcoholics, intestinal absorption is often impaired, and so an even lower rate of absorption must be assumed (Bitsch, 1989). It is therefore essential, particularly for alcoholics, to administer thiamine compounds that are readily absorbed. In the early 1950s, a Japanese team developed a new group of thiamine derivatives (the allithiamines) that met this requirement. Benfotiamine was first synthesized in the early 1960s (Fujiwara, 1954). The extremely high bioavailability of thiamine following administration of the pro-drug benfoti-
amine has been confirmed by many studies. Thus, the superiority of the pharmacokinetic properties of benfotiamine to those of thiamine hydrochloride was shown in animals and humans (Wada, 1961) and the mechanism of uptake and transport of benfotiamine in red blood cells was documented by Shindo (1967). A number of other studies (Fujiwara, 1954; Utsumi, 1962; Thomson, 1971; Baker, 1974; Davis, 1983) showed that the allithiamines are absorbed better, lead to higher thiamine levels in erythrocytes and cerebrospinal fluid, and are retained longer in the body than other water-soluble vitamin B1 derivatives. In absorption experiments in mice and rats with radioactively tagged benfotiamine, clearly higher rates of incorporation into the heart, liver, brain, and diaphragm were found than after oral administration of water-soluble vitamin B1 (Mizuhira, 1968). These results were corroborated by other autoradiographic studies on the incorporation of benfotiamine in mouse organs (Hilbig, 1995).

In bioavailability studies on healthy human subjects, it was shown that absorption of benfotiamine was several times better than that of water-soluble vitamin B1, and that there was a 120-fold higher increase of metabolically active thiamine diphosphate in erythrocytes (Heinrich, 1990). Within a short time, orally administered benfotiamine results in levels of thiamine comparable to those after i.v. administration of water-soluble vitamin B1 salts given at the same dosage. Furthermore, benfotiamine was less toxic than water-soluble vitamin B1 in animal experiments (Bitsch, 1989).

A bioequivalency investigation has produced evidence demonstrating not only the higher bioavailability of benfotiamine, but also the activation of erythrocytic thiamine-dependent transketolase activity, and its activation to thiamine pyrophosphate in vitro (Bitsch et al., 1991). Two additional bioequivalency studies confirmed the significantly better bioavailability of benfotiamine even when compared to the lipophilic thiamine derivatives fursultiamine and thiamine disulphide (Keller-Stanislawski, 1989; Bitsch, 1995).

Thus, benfotiamine fulfils the prerequisite for effective oral treatment of alcoholic polyneuropathy. The present study was designed to examine the therapeutic effectiveness of benfotiamine in marked alcoholic polyneuropathy in comparison with that of a neurotropic B vitamin combination in a formulation that had already proved effective in the treatment of diabetic polyneuropathy (Ledermann and Wiedey, 1989; Stracke et al., 1996).

**PATIENTS AND METHODS**

**Study design and patients**

The experimental design was a three-armed, randomized, multicentre, placebo-controlled double-blind study (benfotiamine in treatment of alcoholic polyneuropathy study, BAP I). Treatment lasted for 8 weeks, with a total of five examinations at 2-weekly intervals (E1 = baseline workup, E5 = final examination).

The following medication was used in the study: (1) benfotiamine (Benfogamma®, Wörwag Pharma GmbH, Stuttgart, Germany) at a dosage of 320 mg/day during weeks 1 to 4 (2 capsules q.i.d.) and 120 mg benfotiamine/day during weeks 5 to 8 (1 capsule t.i.d.); (2) a combination of neurotropic B vitamins (Milgamma® N, Wörwag Pharma GmbH, Stuttgart, Germany), consisting of 320 mg benfotiamine + 720 mg vitamin B6 + 2 mg vitamin B12 for the first 4 weeks (2 capsules q.i.d.), and thereafter 120 mg benfotiamine + 270 mg vitamin B6 + 0.75 mg vitamin B12 (1 capsule t.i.d.); (3) placebo: identical capsules lacking the active components.

After the Ethics Committee of the Landesärztekammer Hessen in Frankfurt am Main, Germany, granted its approval and the patients gave their informed consent, the nine physicians who were involved in the clinical studies assigned a total of 104 out-patients of both sexes, ranging from 30 to 70 years of age, to the three arms of the study: 34 patients to be given benfotiamine alone, 35 patients to be given the neurotropic B vitamin formulation, and 35 patients to be given placebo. The study was strictly monitored according to the GCP international standards by the US Clinical Research Organization (CRO: Institut für Klinische Forschung Dr Wiedey GmbH, Zeppelinstr. 5, Konstanz, Germany).

The criteria for admission to the study were: (1) alcoholism as defined by DSM-III-R; at least three of the criteria were required; and (2) alcoholic polyneuropathy with vibration perception thresh-
old at the great toe ≤2, pain score ≤3, and sensory score ≤1. These inclusion criteria ensured that only patients with marked symptoms of alcoholic polyneuropathy were admitted to the study. All patients (including those who received placebo) were instructed not to change their drinking habits during the study.

Patients with allergies to any of the constituents of the drugs under study, diabetes mellitus, alcoholic polyneuropathy of long duration (>8 years), Parkinson’s disease, toxic neuropathy of non-alcoholic origin, known neurologic conditions, endocrinological disorders, psychiatric disorders, collagenosis, skin eruptions in the regions of assessment, poor overall condition, drug dependency, pregnancy or lactation, or vitamin replacement within the previous 4 weeks were excluded, as were patients participating in other studies.

Assessment of peripheral nerve function

At randomization (E1), after 2 weeks (E2), 4 weeks (E3), 6 weeks (E4), and 8 weeks (E5), data on the following parameters of peripheral nerve function were recorded. Vibration perception thresholds (biothesiometry) at the great toe (the major objective criterion), inside ankle, metatarsal bone, and mid-tibia were determined using a graduated tuning fork according to the method of Rydel and Seiffer (8/8 scale; Claus et al., 1988; Thivolet et al., 1990). The endpoint was the time elapsed until the patient no longer perceived the vibration of the tuning fork. A vibration threshold of 8 was defined as normal, and 0 corresponded to severe impairment. The arithmetic mean was determined from three individual measurements.

The intensity of pain, a major subjective criterion, was assessed by McGill’s pain questionnaire (ppi scale: 5 = no pain, 0 = devastating pain; Melzack, 1984).

Scoring for motor function involved the degree of paralysis (5 = normal, 0 = total inactivity), sensory function (2 = no impairment, 0 = impaired perception of touch distally and proximally to the ankle), co-ordination (2 = no impairment, 0 = evident ataxis) and reflexes (2 = no impairment, 0 = absence or weakening of the Achilles tendon reflex and other reflexes), and was done according to frequently used assessment scales.

An overall score describing the severity of polyneuropathy symptoms was obtained by adding the data for individual parameters (16 = free of symptoms, 0 = maximum clinical expression). Scores ≥10 are indicative of a less severe clinical picture.

The ‘clinical global impression’ (CGI) was based on a questionnaire from the Collegium Internationale Psychiatriae Scalarum (1986).

Laboratory evaluation

At the beginning and end of the investigation, the following laboratory studies were completed, using standard methods: serum glutamate-oxaloacetate aminotransferase or aspartate aminotransferase (SGOT), serum glutamate-pyruvate aminotransferase or alanine aminotransferase (SGPT), γ-glutamyltransferase (GGT), alkaline phosphatase, triglycerides, cholesterol, creatinine, blood alcohol, fasting blood sugar and sedimentation rate after 1 and 2 h.

Statistical analysis

The required number of patients was estimated on the basis of a study on diabetic polyneuropathy (Lederman and Wiedey, 1989), in which the endpoint variable, vibration perception threshold at the tip of the great toe as measured with a tuning fork by the method of Rydel and Seiffer, was found to increase by an average of 1.38 units. Assuming that the improvement of vibration perception threshold in the alcoholic polyneuropathy under treatment would be of a similar magnitude, a sample size of 22 patients in each group was determined (α = 0.05, β = 0.20). The sample size was raised to 25 per group in order to make up for loss of discrimination by the transition from parametric to non-parametric methods. On the assumption that the dropout rate could be ~25%, the number of cases was further raised to 35 patients in each group.

For biometric analysis, comparison of treatment groups was undertaken using the $\chi^2$-test for contingency tables for discrete variables and using variate analysis for continuous variables. The level of significance was defined as a probability of error of $P = 0.05$. Means, SD and 95% confidence intervals were used for description.
Table 1. Homogeneity of the patient groups

<table>
<thead>
<tr>
<th>Variable at initial randomization</th>
<th>Placebo</th>
<th>Neurotropic B vitamin formulation</th>
<th>Benfotiamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>65.5</td>
<td>74.2</td>
<td>71.9</td>
</tr>
<tr>
<td>Daily alcohol consumption of &gt;200 g (%)</td>
<td>44.8</td>
<td>58.1</td>
<td>48.4</td>
</tr>
<tr>
<td>Alternating constipation and diarrhoea (%)</td>
<td>62.1</td>
<td>64.5</td>
<td>62.5</td>
</tr>
<tr>
<td>Pain intensity score (≤3)* (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Motor function score (≤3)** (%)</td>
<td>75.9</td>
<td>74.2</td>
<td>68.8</td>
</tr>
<tr>
<td>Coordination score (≤1)** (%)</td>
<td>82.8</td>
<td>77.4</td>
<td>62.5</td>
</tr>
<tr>
<td>Sensory function score (=0)** (%)</td>
<td>62.1</td>
<td>64.5</td>
<td>68.7</td>
</tr>
<tr>
<td>Reflexes score (≤1)** (%)</td>
<td>58.6</td>
<td>74.2</td>
<td>68.8</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.6</td>
<td>54.6</td>
<td>52.0</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>76.6</td>
<td>76.5</td>
<td>74.5</td>
</tr>
<tr>
<td>Duration of polyneuropathy (years)</td>
<td>2.19</td>
<td>2.61</td>
<td>1.91</td>
</tr>
<tr>
<td>Vibration perception threshold (graduated tuning fork)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tip of right great toe</td>
<td>0.762</td>
<td>0.765</td>
<td>0.791</td>
</tr>
<tr>
<td>Tip of left great toe</td>
<td>0.772</td>
<td>0.765</td>
<td>0.756</td>
</tr>
</tbody>
</table>

*Pain intensity according to McGill (5–0); **according to assessment scales.

RESULTS

Homogeneity of the patient groups

A review of the criteria for inclusion and exclusion at biometric evaluation revealed that 12 of the patients did not fulfill all inclusion criteria; these patients were therefore not evaluated. A further eight patients did not complete the study; however, their withdrawal had no apparent connection with the treatment regimen. Thus, the following data are based on the 84 patients who completed the entire study (benfotiamine group, n = 30; neurotropic B vitamin formulation group, n = 26; placebo group, n = 28).

For evaluation of the homogeneity of the patient groups after randomization, a total of 28 discrete and 24 continuous variables were assessed. Some of the data are given in Table 1. None of the variables was found to be significantly different between the groups at baseline examination; this is also true of the variables not listed in Table 1.

Changes in vibration perception

Tip of great toe. During the treatment period, vibration perception improved in all three groups, regardless of whether it was assessed on the left or right side (Table 2). Figure 1 depicts the data for the right great toe. The vibration perception thresholds in the placebo and neurotropic B vitamin groups were nearly identical. For this reason, the data of these two groups were combined in order to raise the number of cases, and compared with those of the benfotiamine group by means of variate analysis.

Benfotiamine proved to be significantly more effective (P = 0.040) than the neurotropic B vitamin formulation and placebo. At the end of treatment, vibration perception was still noticeably impaired in all treatment groups.

Medial ankle, metatarsal bone, and mid-tibia. In all three therapy arms, there was a steady improvement of vibration perception at the medial ankle, the metatarsal bone, and mid-tibia (on both the right and left sides) until the end of the study period. At all measurement sites, the most marked improvement was found at E5 in the group treated with benfotiamine; Table 3 shows the data for the right and left medial ankles as an example. Despite the increased success with benfotiamine treatment, the results did not reach statistical significance. Similarly beneficial, but likewise not statistically significant, effects were also found in the courses of vibration perception threshold at the metatarsal bones and mid-tibia (data not shown).
Table 2. Improvement of vibration perception units at the tip of the great toe

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Initial assessment (E1)</th>
<th>Final assessment (E5)</th>
<th>Improvement (units)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, right side (n = 28)</td>
<td>0.79 ± 0.29</td>
<td>2.25 ± 0.52</td>
<td>1.46</td>
</tr>
<tr>
<td>Placebo, left side (n = 28)</td>
<td>0.80 ± 0.29</td>
<td>2.30 ± 0.53</td>
<td>1.50</td>
</tr>
<tr>
<td>Neurotropic B vitamin formulation, right side (n = 26)</td>
<td>0.73 ± 0.26</td>
<td>2.30 ± 0.61</td>
<td>1.57</td>
</tr>
<tr>
<td>Neurotropic B vitamin formulation, left side (n = 26)</td>
<td>0.71 ± 0.26</td>
<td>2.04 ± 0.53</td>
<td>1.33</td>
</tr>
<tr>
<td>Benfotiamine, right side (n = 30)</td>
<td>0.77 ± 0.26</td>
<td>2.89 ± 0.61</td>
<td>2.12</td>
</tr>
<tr>
<td>Benfotiamine, left side (n = 30)</td>
<td>0.75 ± 0.27</td>
<td>2.91 ± 0.58</td>
<td>2.16</td>
</tr>
</tbody>
</table>

E1 was performed at randomization, whereas E5 was after 8 weeks of treatment. Values are means ± SD. *Mean of units of the graduated tuning fork.

Effect on pain intensity

Intensity of pain decreased in all treatment groups during the 8-week therapy course. At the conclusion of treatment, considerably more of the patients taking benfotiamine (77%) were free of pain or had only mild complaints than in the comparison groups (54% in each; Fig. 2). However, the apparently better results under benfotiamine still did not reach statistical significance (P = 0.31).

Effect on motor function (degree of paralysis)

The patients in the benfotiamine group had a significantly lower degree of paralysis than those on placebo (P = 0.038). In 64.3% of the patients taking placebo, 73.1% of those taking the neurotropic B vitamin formulation and 90% of those taking benfotiamine, motor function was impaired only slightly or not at all at final assessment of the study (Fig. 3).

Effect on co-ordination, sensory function and reflexes

At the end of the study, 60.7% of the patients in the placebo group, 53.9% of those on the neurotropic B vitamin formulation, and 80% of those on benfotiamine had no impairment (P = 0.093). Assessment of sensory function and reflexes revealed no differences that could be attributed to treatment.

Effect on the overall neuropathy score

At the end of the study, 67.9% of the placebo patients, 76.9% of the patients taking the neurotropic B vitamin formulation, and 93.3% of those on benfotiamine had scores of 10 or more. The superior outcome of treatment with benfotiamine was statistically significant (P = 0.39; Fig. 4).

Clinical global impressions

When the severity of disease, therapeutic effectiveness, and estimate of change of the overall situation at the end of the study were assessed, benfotiamine was judged clearly superior to the other two treatment groups. However, the beneficial effect of benfotiamine treatment did
Table 3. Improvement of vibration perception threshold at the medial ankle

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Initial assessment (E1)</th>
<th>Final assessment (E5)</th>
<th>Improvement (units)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, right side</td>
<td>1.32 ± 0.49</td>
<td>2.64 ± 0.58</td>
<td>1.32</td>
</tr>
<tr>
<td>Placebo, left side</td>
<td>1.28 ± 0.52</td>
<td>2.94 ± 0.70</td>
<td>1.66</td>
</tr>
<tr>
<td>Neurotropic B vitamin formulation, right side</td>
<td>1.32 ± 0.48</td>
<td>2.77 ± 0.63</td>
<td>1.45</td>
</tr>
<tr>
<td>Neurotropic B vitamin formulation, left side</td>
<td>1.23 ± 0.53</td>
<td>2.68 ± 0.60</td>
<td>1.45</td>
</tr>
<tr>
<td>Benfotiamine, right side</td>
<td>1.24 ± 0.48</td>
<td>3.08 ± 0.55</td>
<td>1.84</td>
</tr>
<tr>
<td>Benfotiamine, left side</td>
<td>1.31 ± 0.47</td>
<td>3.18 ± 0.58</td>
<td>1.87</td>
</tr>
</tbody>
</table>

For definitions of E1 and E5, see Table 2. Values are means ± SD. * Mean units of the graduated tuning fork.

not reach statistical significance.

**Compliance and side-effects**

Three patients had to be reminded to improve their compliance, but it was not necessary to remove them from the study. Apart from this, compliance was considered in line with the study plan. No adverse events related to treatment occurred.

**Laboratory results**

All parameters examined at the start and finish of the study showed a statistically non-significant trend toward diminished levels.

**DISCUSSION**

The literature shows that thiamine levels are frequently diminished in alcoholics and patients with alcoholic polyneuropathy (Heimann and Naumann, 1981; Meyer, 1981; Bachevalier, 1981; Waldenlind, 1981; Woelk, 1982; Posthuma, 1983); however, controlled, double-blind interventional studies in alcoholic polyneuropathy have not been published until now.

In addition to correcting vitamin B₁ deficiency, therapeutic administration of thiamine may also produce some pharmacological effects. In animals given dosages that exceeded basic requirements by 100- or 1000-fold thiamine has analgesic and neuroprotective effects (Woelk and Peiler-Ichikawa, 1985; Jurna, 1988; Reeh, 1988, 1991; Wild, 1988). However, if high levels are to be achieved with oral vitamin B₁ treatment, lipid soluble thiamine derivatives or pro-drugs with high bioavailability, such as benfotiamine, are required. Benfotiamine fulfils the pharmacokinetic...
BENFOTIAMINE IN ALCOHOLIC POLYNEUROPATHY

30

Beafotiajnine Neurotronic

B vitamin

formulation

Placebo

Fig. 4. Percentage of patients with an overall score of polyneuropathy symptoms of \( \geq 10 \) at the conclusion of the study. \( *P = 0.039 \).

requirements for effectiveness essential for successful oral vitamin B\(_1\) therapy.

The results of the present investigation have demonstrated the effectiveness of monotherapy with the pro-drug benfotiamine in alcoholic polyneuropathy. Within the 8-week study period, benfotiamine led to a significant improvement of the threshold of vibration perception at the great toe, motor function, and the overall symptom score. Marked improvement occurred in both pain and co-ordination.

In the present study, the combined formulation produced no statistically significant effect. Since the benfotiamine content of both active formulations was identical, the explanation is conjectural. Perhaps in alcoholic polyneuropathy, the addition of vitamins B\(_6\) and/or B\(_12\) counteracted the favourable effects of benfotiamine. This contrasts with the results achieved in diabetic polyneuropathy, in which both the combined formulation (Ledermann and Wiedey, 1989; Stracke et al., 1996) and benfotiamine alone (Haupt, 1995) produced statistically significant beneficial effects. The lack of effectiveness in the present study of the combined formulation suggests that diabetic and alcoholic polyneuropathies may have different modes of pathogenesis. In alcoholic polyneuropathy, the primary cause might conceivably involve a thiamine deficiency, which can be successfully overcome with oral benfotiamine. Additional studies are required in order to clarify these as yet unanswered questions of pathogenesis and mode of action. The results of the present BAP I study, by demonstrating the effectiveness of benfotiamine in polyneuropathy of alcoholism, where intestinal mucosa is often damaged and active transport of thiamine impaired, illustrates that the use of the lipophilic pro-drug benfotiamine is imperative in alcoholism.

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