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Benfotiamine in the treatment of diabetic polyneuropathy – a three-week randomized, controlled pilot study (BEDIP Study)

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diabetic polyneuropathy – neuropathy score – benfotiamine treatment

Abstract. Objective: The aim of the study was to evaluate the efficacy of benfotiamine administered over three weeks (allithiamine; a lipid-soluble vitamin B_1 prodrug with high bioavailability) to patients with diabetic polyneuropathy in a randomized, placebo-controlled, double-blind, two-center pilot study. Material and methods: Forty inpatients (23 male, 18 female, age range 18 – 70 years) with a history of type 1 or 2 diabetes and polyneuropathy of not longer than two years, were included in the study. Twenty Patients received two 50 mg benfotiamine tablets four times daily and 20 patients received placebo over the three-week study period. Two clinical units were involved with 10 patients receiving placebo and 10 patients benfotiamine in each. The neuropathy score according to Katzenwadel et al. [1987] was used to evaluate symptoms of polyneuropathy, vibration perception threshold and both the physician's and the patient's own assessment were documented. Results: A statistically significant ($p = 0.0287$) improvement in the neuropathy score was observed in the group given active drug when compared to the placebo-treated controls. There was no statistically significant change observed in the tuning fork test. The most pronounced effect on complaints was a decrease in pain ($p = 0.0414$). More patients in the benfotiamine-treated group than in the placebo group considered their clinical condition to have improved ($p = 0.052$). No side effects attributable to benfotiamine were observed. The differences between the groups cannot be attributed to a change in metabolic parameters since there were no significant alterations in the HbA_1 levels and blood sugar profiles. The body mass index of the two groups did not differ. Conclusion: This pilot investigation (BEDIP Study) has confirmed the results of two earlier randomized controlled trials and has provided further evidence for the beneficial effects of benfotiamine in patients with diabetic neuropathy.

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Introduction

Diabetic neuropathy is a well-known complication in patients with diabetes mellitus, although its clinical and prognostic importance has been recognized only in the last few decades. The main symptoms of dysesthesia and pain substantially reduce the quality of life of the patient [Benbow et al. 1998]. Hypesthesia, which is a key component in neuropathy, may lead to the development of trophic ulcers, gangrene and amputation of the leg. Today, diabetic neuropathy is considered a prime pathogenetic factor in the diabetic foot syndrome [Boulton 2003, Jermendy 2002]. The poor prognosis of autonomic [Coppini et al. 2000, Ziegler 1994] and peripheral neuropathy [Forsblom et al. 1998] has been shown in prospective studies.

Since vitamin B_1 counteracts disorders in nerve function, thiamine salts are often used to treat diabetic polyneuropathy. However, the bioavailability of orally administered, water-soluble, thiamine compounds at the dose rates commonly used (50 – 100 mg) is only 4 – 6% [Heinrich 1990].

In the early 1950s, Fujiwara [1954] discovered a new group of lipid-soluble thiamine derivatives called allithiamines and one of these, allithiamine benfotiamine, was considered to be more effective than the thiamine drugs used earlier.

When given orally at an equivalent dosage, allithiamine benfotiamine raises thiamine levels in blood and tissues much more than water-soluble thiamine salts and it has been shown recently that benfotiamine can inhibit three of the major biochemical pathways implicated in the pathogenesis of

hyperglycemia-induced vascular damage, i.e. the hexosamine pathway, the advanced glycation endproduct/AGE/ formation pathway and the diacylglycerol/DAG/protein kinase C/PJC/pathway, by activating transketolase in the pentose phosphate pathway [Hammes et al. 2003].

Two double-blind, placebo-controlled studies carried out in Germany previously have demonstrated a statistically significant improvement in pain, dysesthesia, vibration perception and nerve conduction velocity in patients with diabetic polyneuropathy on oral treatment with a combination of benfotiamine, vitamin B_6 and B_{12} [Ledermann and Wiedey 1989, Stracke et al. 1996]. The aim of this double-blind, randomized, placebo-controlled clinical pilot study was to investigate the influence of benfotiamine alone on neuropathy symptoms in patients with diabetic neuropathy.

Study design and patients

The study was named the "Benfotiamine in the Treatment of Diabetic Polyneuropathy (BEDIP) study" and comprised a randomized, placebo-controlled, bicentric, double-blind pilot study, involving a three-week treatment period. A washout phase was not necessary since patients had not been taking medications over a long enough period to have an effect on the neuropathy symptoms. The coated tablets contained 50 mg benfotiamine. The placebo medication was identical in appearance but contained no benfotiamine. The dosage of each medication was two tablets four times daily. The study was carried out according to the GCP rules and 40 patients gave their informed consent and were admitted to the study using the following inclusion criteria: insulin-treated, type 1 or type 2 diabetes (both male and female subjects were admitted to the study), age 18 – 70 years, manifest symptoms involving symmetrical distal diabetic polyneuropathy of not longer than two years duration, no previous prolonged therapy of polyneuropathy and no vitamin supplementation within four weeks of commencement of the study. The study was begun in 1991, three years prior to introduction of the law (5th Amendment) on Ethics Committee approval for clinical studies. For comparison, in 1997 Ethics Committee approval was given by the Bavarian Chamber of Medicine for a similar, double-blind, randomized, placebo controlled study with benfotiamine involving a 4-week vitamin-B free run-in period in patients with symptomatic diabetic polyneuropathy.

Patients with any of the following criteria were excluded from the study: known allergy to benfotiamine, neuropathy of other origin than diabetes, known underlying neurological disease, impaired arterial circulation in the lower extremities, unstable course of diabetes mellitus, endocrine disorders, collagen disease, skin eruptions in the region of assessment, pregnancy or lactation, alcohol and drug abuse, poor overall physical and mental condition, renal failure (serum creatinine $\geq$ 3 mg/100 ml), liver dysfunction (hepatic enzymes, > 100% above normal), malignant tumors, cytotoxic and immunosuppressive therapy.

Twenty inpatients in each of two hospitals the "Saale-Klinik (Bad Kissingen)" and the "Eleonorenklinik (Lindenfels)" were randomly assigned to receive either benfotiamine or placebo. The investigators and patients were "blinded" to the randomization of the drug assignments.

Methods

The patients were examined at the beginning of the study (E1) and on every third day over three weeks (E2 = 4, E3 = 7, E4 = 11, E5 = 15, E6 = 18, E7 = 21 days after starting application). Symptoms and signs were evaluated using a neuropathy score [Katzenwadel et al. 1987]. The following symptoms and signs of neuropathy were scored semiquantitatively (graded 0 – 2, see Table 2): motor function (no impairment, slight paralysis, marked paralysis or atrophy), sensory function (reaction to touch stimuli, discrimination between pointed and blunt stimuli, recognition of numbers written on the skin).

The symptoms of pain recorded as: no complaints, tolerable hyper- and dysesthesias, e.g. formication, piercing pain, "burning feet". Deep muscle reflexes recorded included the biceps reflex, patellar reflex and Achilles tendon reflex). Tests for coordination of movement involved the finger-nose test, the knee-heel test and evaluation of gait.

No overall impairment was scored as 0 and the highest impairment as 10.

Vibration perception threshold (secondary endpoint): Assessment of the vibration perception threshold on the upper extremities (tip of index finger, extensor side of 2nd metacarpal, middle of radius) and on the lower extremities (tip of large toe, extensor side of 1st metatarsal, middle of tibia) was performed with a calibrated (quantitative) 8/8 scale tuning fork (Rydel and Seiffer).

Laboratory data: HbA_1, SGOT, SGPT, γ-GT, alkaline phosphatase, cholesterol, triglycerides, creatinine and erythrocyte sedimentation rate were determined at E1 and E7. Blood sugar profiles with pre-prandial and post-prandial values were obtained on two days each week.

Statistical evaluation: Homogeneity of the groups was determined using the χ^2–test and Wilcoxon's U-test. Analysis of variances was used to compare the "treated" and "placebo" groups. Results for each of the various parameters are shown as their respective medians and arithmetic means. Range and 95% confidence intervals indicate range of variance. The level of significance was defined as a probability of error of $\alpha = 0.05$.

Table 1. Clinical characteristics of patients on admission to the study.

	Placebo group	Active drug group
Number	20	20
Gender (m/f)	11/9	12/8
Age (years)	52.5 (27 – 66)	52 (38 – 58)
Weight (kg)	86.5 (53 – 107)	82 (64 – 100)
Duration of neuropathy (months)	13 (4 – 24)	13 (6 – 24)
HbA_1 (%)	9.4 (7.1 – 11.8)	9.85 (6.7 – 12.7)

Median (min. – max.) or number of patients

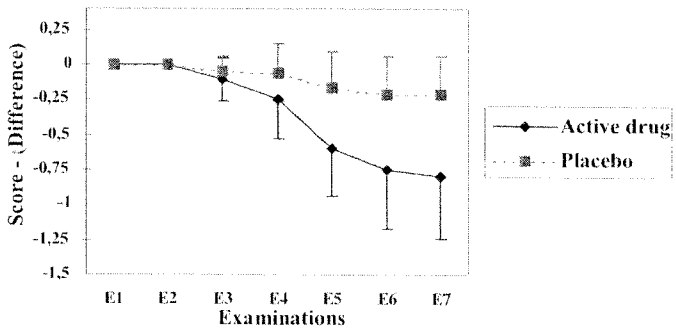

Figure 1. Changes in the neuropathy score in the course of the study (means and standard deviations of differences from the baseline score at E1).

Results

Of the 40 patients included, 38 completed the study protocol. Two patients in the placebo group dropped out. Demographic data of the two groups are presented in Table 1. There were no relevant differences in gender distribution, age, height and weight among the groups.

The HbA_1 levels improved slightly in both the treated (E1 10.56 ± 1.94; E7 9.18 ± 1.48) and placebo (E1 9.56 ± 1.2; E7 8.88 ± 0.88) groups and there was no statistical difference between the groups. Blood sugar profile measurements demonstrated that there were no statistical differences between the two groups both before commencement of the

Table 2. Score for diagnosis of peripheral neuropathy. After Katzenwadel et al. [1987].

Points	Motoric function	Pain history	Sensory function	Coordination	Reflexes
0	Unimpaired	No complaints	Unimpaired	Unimpaired	Unimpaired
1	Slight paralysis	Tolerable hyper- and dysesthesias, e.g. formication	Sharp-dull discrimination impaired	Finger-nose coordination impaired	Achilles reflex absent or weakened
2	Marked paralysis, atrophy	"Piercing pain", "burning" foot-soles	Marked impairment over wrists and ankles, extending proximally	Additionally gait impairment	Absence or weakening of other reflexes

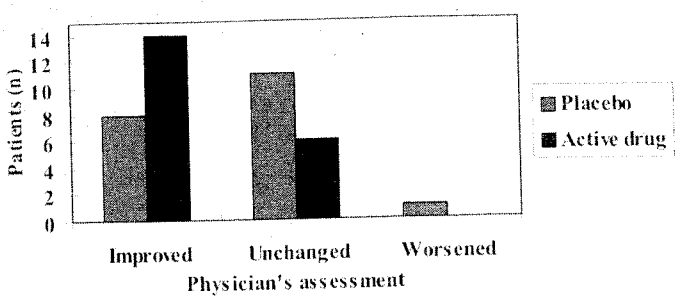

Figure 2a. Assessment of effectiveness by physician (absolute frequency).

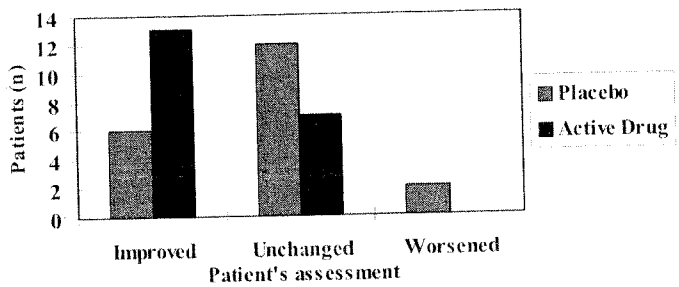

Figure 2b. Assessment of effectiveness by patient (absolute frequency).

trial and after the trial was completed. The slight improvement during the clinical trial was not statistically significant. There were no significant differences in body mass index (BMI) between the treated and placebo groups (29.2 ± 8.83 versus 28.4 ± 4.32, respectively).

Neuropathy score

Score differences between the two groups during the study are shown in Figure 1. Compared to baseline values, the improvement in the neuropathy score was significantly more pronounced in the group receiving active drug than in the control group ($p = 0.02$). Although the baseline scores of the two groups differed slightly, this has only a minor effect on the statistical comparison. The major factor showing improvement in the neuropathy score was the change in pain relief ($p < 0.05$) in the patients receiving benfotiamine. Although there was a tendency to an improvement in sensory nerve function in the benfotiamine group, this change was not statistically significant compared to the placebo group.

There was no significant improvement in the neuropathy score in both the benfotiamine group and the placebo group. However, the pain relief index was significantly improved in the benfotiamine group using both a within-group and a between-group comparison.

The power for the comparison within the benfotiamine group was sufficient (> 80%) but that for the between group comparison was not.

Vibration perception threshold

Although the vibration perception threshold changed in both groups, there was no statistically significant difference between groups.

Assessment by physician and patient

At the final examination (E7), both physician and patient evaluated the therapeutic effectiveness using the categories "improved", "unchanged" or "worsened". Figure 2a shows the assessment by the physician and Figure 2b the assessment by the patient. Benfotiamine was judged to be more effective by both physicians ($p = 0.128$) and patients ($p = 0.052$) when compared to placebo.

Discussion

High doses of a benfotiamine/vitamin B_6 in combination with B_{12} has been proven efficacious in diabetic polyneuropathies irrespective of whether signs of vitamin deficiency were detectable in peripheral blood [Hashizume 1980, Reiners and Haupt 1996]. In experimental models, analgetic and neurotropic effects occurred only when the dose taken was 100- to 1000 times greater than the amounts consumed with a normal food intake [Reeh 1991, Wild 1988]. Oral treatment with water-soluble vitamin B_1 has been found unsatisfactory because of the limited absorption and low storage capability of the body [Heinrich 1990]. In the early 1950s, however, Japanese researches developed a new lipid-soluble group of thiamine preparations called

allithiamines and benfotiamine is a derivative of this class of agents.

Benfotiamine (S-benzoyl-o-monophosphate) is a thiamine prodrug belonging to the class of allithiamines [Fujiwara 1954]. The uptake and transport mechanisms in erythrocytes have been elucidated [Shindo 1967] and several animal and human studies have confirmed that the bioavailability of benfotiamine is superior to water-soluble thiamine salts when given orally, blood levels are higher and the drug persists longer in blood, erythrocytes and cerebrospinal fluid [Baker 1974, Davis 1983, Fujiwara 1954, Thomson 1971]. Using radioactively labeled drugs given orally to mice and rats, the incorporation of benfotiamine in heart, liver, brain and diaphragm was greater than that of water-soluble thiamine [Nakajima 1968, Reeh 1991].

In animal experiments benfotiamine is less toxic (LD_{50}) than water-soluble thiamine hydrochloride [Bitsch 1989]. In a bioequivalence study in humans, the absorption of benfotiamine was several times greater than that of water-soluble vitamin B_1 and the rise in the metabolically active thiamine-diphosphate concentration in erythrocytes was 120 times higher [Heinrich 1990]. Benfotiamine significantly improved the activation of thiamine-dependent transketolase in erythrocytes [Bitsch 1991] and this effect was superior to that of other thiamine derivatives such as lipophylic fursultiamine and thiamine disulfide [Bitsch 1995]. Recent data have shown that using equimolar quantities the bioavailability of benfotiamine is ten times higher than that of thiamine mononitrate [Schreeb et al. 1997]. A comparative trial demonstrated that benfotiamine was the most potent thiamine derivate tested [Greb and Bitsch 1998].

In a placebo-controlled, double-blind study, benfotiamine combined with vitamin B_6 and B_{12} significantly improved pain and sensory function [Ledermann and Wiedey 1989], and the same treatment in 24 insulin-dependent diabetic patients with overt polyneuropathy also produced favorable changes. Stracke et al. [1996] found a 30% reduction in sensory vibration thresholds at the second metacarpal and metatarsal bones in contrast to a slight rise under placebo. The effects of therapy on nerve conduction velocity in this latter investigation were even more marked showing an increase in the peroneal nerve and a decrease under placebo. Further beneficial effects of various benfotiamine regimens in diabetic patients with polyneuropathy have been reported by Winkler et al. [1999]. A significant improvement in sensory nerve function with benfotiamine has been reported in the case of symptom-free, diabetic adolescents with hypesthesia [Barkai et al. 1998] and improvements in autonomic function after therapy with benfotiamine have been observed in an experimental study [Koltai et al. 1997].

In the pilot study reported here, a three-week treatment with benfotiamine resulted in a statistically significant decrease of the neuropathy score of nearly one unit (difference between test and placebo group), together with a therapeutically relevant relief of neuropathic pain ("shooting" pain and "burning" feet) and a higher rating score by physician and patient versus group. There was no significant improvement in the vibration threshold and this may be because the study was of limited duration. However, it should be noted that clinical improvement is probably the most important measure of outcome, as was the case in the large multicenter ALADIN trial [Ziegler et al. 1995].

It is of interest that in rats with streptozotocin-induced diabetes, benfotiamine markedly inhibited neural imidazole-type AGE formation (advanced glycation endproducts) and completely prevented occurrence of diabetes-induced glycation products [Stracke et al. 2001]. Moreover, thiamine pyrophosphate and pyridoxamine potently inhibited the formation of AGEs and were more effective than aminoguanidine [Booth et al. 1996].

Recent reports have demonstrated that benfotiamine inhibits the hexosamine pathway, AGE formation and the diaglycerol (DAG)/protein kinase C (PKC) pathway by activating the pentose phosphate pathway enzyme transketolase [Hammes et al. 2003]. This is of considerable interest with regard to the findings in the present study and previous studies because the pathomechanism of diabetic microvascular complications is thought to involve alterations in these pathways. Hammes et al. [2003] demonstrated that benfotiamine treatment also prevents diabetic retinopathy and the authors concluded that the ability of benfotiamine to inhibit the three forementioned pathways simultaneously might be associated with its therapeutic ef-

fects in preventing the development and progression of diabetic complications. Taken together, the results discussed here indicate that benfotiamine has a therapeutic action at the pathogenetic level in diabetic neuropathy [Jermendy and Kempler 2002, Stracke 1995].

Conclusion

The therapeutic effects of benfotiamine on neuropathic pain and sensory functions in diabetic neuropathy, which may have a pathogenetic basis involving transketolase in the pentose phosphate pathway, have been confirmed in this study (BEDIP Study) which is the third randomized controlled trial of this type showing beneficial effects of benfotiamine in such patients.

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