

Benfotiamine in Diabetic Polyneuropathy (BENDIP): Results of a Randomised, Double Blind, Placebo-controlled Clinical Study

Authors

H. Stracke¹, W. Gaus², U. Achenbach³, K. Federlin¹, R.G. Bretzel¹

Affiliations

¹ Medical Clinic und Policlinic III, University Hospital Giessen and Marburg, Location Giessen, Germany

² Institute for Biometrics, University Ulm, Germany

³ Wörwag Pharma GmbH & Co. KG, Böblingen, Germany

Key words

- diabetic polyneuropathy
- benfotiamine
- advanced glycation end products
- glucose metabolism

Abstract



Aim: Efficacy and safety of benfotiamine in treatment of diabetic polyneuropathy.

Methods: Double blind, placebo-controlled, phase-III-study. 181 patients were screened. 165 patients with symmetrical, distal diabetic polyneuropathy were randomised to one of three treatment groups entering the wash-out phase and 133/124 patients were analysed in the ITT/PP analysis: Benfotiamine 600 mg per day (n=47/43), benfotiamine 300 mg per day (n=45/42) or placebo (n=41/39).

Results: After 6 weeks of treatment, the primary outcome parameter NSS (Neuropathy Symptom Score) differed significantly between the treat-

ment groups (p=0.033) in the PP (per protocol) population. In the ITT (intention to treat) population, the improvement of NSS was slightly above significance (p=0.055). The TSS (Total Symptom Score) showed no significant differences after 6 weeks of treatment. The improvement was more pronounced at the higher benfotiamine dose and increased with treatment duration. In the TSS, best results were obtained for the symptom "pain". Treatment was well tolerated in all groups.

Conclusion: Benfotiamine may extend the treatment option for patients with diabetic polyneuropathy based on causal influence on impaired glucose metabolism. Further studies should confirm the positive experiences.

received 28.11.2007

first decision 08.01.2008

accepted 11.03.2008

Bibliography

DOI 10.1055/s-2008-1065351

Published online:

May 13, 2008

Exp Clin Endocrinol Diabetes
2008; 116: 600–605

© J. A. Barth Verlag in

Georg Thieme Verlag KG

Stuttgart · New York

ISSN 0947-7349

Correspondence

Prof. Dr. H. Stracke

University Hospital Giessen and

Marburg GmbH

Medical Clinic and Policlinic III

Rodthohl 6

35392 Giessen

Germany

Tel.: + 49/641/994 27 54

Fax: + 49/641/994 27 69

Hilmar.Stracke@innere.med.

uni-giessen.de

Abbreviations



AGEs	advanced glycation end products
ATP	according to protocol
BEDIP	Benfotiamine in the treatment of Diabetic Polyneuropathy
cm	centimetre
CRF	case report form
DNA	deoxyribonucleic acid
GCP	good clinical practice
HbA _{1c}	haemoglobin A _{1c}
ITT	intention to treat
kg	kilogram
mg	milligram
n	number
LOCF	Last Observation Carried Forward
NDS	Neuropathy Disability Score
NFκ _B	nuclear factor κ _B
nNOS	neuronal nitric oxide synthase
NSS	Neuropathy Symptom Score
NTSS-6	Neuropathy Total Symptom Score-6
p	probability
PP	per protocol

RAGE

receptor for advanced glycation end products

TSS

Total Symptom Score

Introduction



Diabetes is a worldwide threat with continuously increasing incidence and prevalence. In Germany, approximately 7% of the population suffers from diabetes, i.e. at least 6 million people. Polyneuropathy is found in about 30–50% of diabetic patients. In a recent cost calculation it was found that the costs of diabetic neuropathy are usually underestimated though they are in the same range as the costs of diabetes-associated cardiovascular diseases (Herholz, 2006).

Pathophysiology of diabetic complications like neuropathy includes the formation of advanced glycation end products (AGEs), increased activity of the polyol and the hexosamine pathway of glucose metabolism as well as activation of protein kinase C with the common feature of overproduction of superoxide by the mitochondrial

electron transport chain (Brownlee, 2001). Recently it was shown that pathophysiological changes of binding of ligands to the receptor for advanced glycation end products (RAGE) occur already at the stage of impaired glucose tolerance, suggesting that activation of the RAGE pathway may be one of the first steps in the pathogenesis of diabetic polyneuropathy (Haslbeck et al., 2005).

Effective treatment of diabetic neuropathy as early as possible is essential in order to slow progression of the disease. However, apart from optimisation of blood glucose control, there are only limited causal therapeutic options. Even with optimal blood glucose control (HbA_{1c} $6.7 \pm 1.9\%$) 28% of insulin-dependent patients showed diabetic neuropathy in a large Europe-wide study (Tessfaye et al., 1996).

Recently it was shown that diabetic patients are subject to considerable vitamin B1 deficiency (Thornalley et al., 2007). In a comparison between diabetic patients (26 type 1, 48 type 2 diabetes) and normal healthy volunteers, decreased plasma levels of vitamin B1 by 76 or 75%, respectively, were found in the diabetic patients. This was explained by a 24- or 16-fold increase in renal clearance of thiamine. Furthermore, increased thiamine transporter content of the erythrocytes, explaining the contradictory results on vitamin B1 deficiency in diabetic patients so far, masked the conventional assessment of thiamine status.

In alcoholics, vitamin B1 deficiency as cause of polyneuropathy symptoms is already known for long time. These symptoms can be treated by supplementation of lipid soluble thiamine derivatives like benfotiamine (Woelk et al., 1998). Also in diabetic polyneuropathy, clinical studies with benfotiamine have been performed with promising results, either in monotherapy (Haupt et al., 2005; Schmidt, 2002) or in combination with vitamin B6 and/or vitamin B12 (Winkler et al., 1999; Stracke et al., 1996; Ledermann and Wiedey, 1989). Experimental data showed that benfotiamine blocks several pathways of hyperglycaemic damage, i.e. the hexosamine pathway, the formation of AGEs, the activation of protein kinase C and the activation of $\text{NF-}\kappa\text{B}$ by activation of transketolase, the rate limiting enzyme of the non-oxidative branch of the pentose phosphate pathway (Hammes et al., 2003). Furthermore, it prevents AGE-induced micro- and macrovascular endothelial dysfunction (Stirban et al., 2006). Therefore, benfotiamine is a therapeutic option based on a pathogenetic concept (Ziegler and Bierhaus, 2007).

The aim of this study was to verify the effect of benfotiamine as monotherapy in a larger population of patients with diabetic neuropathy in a double blind, randomised, placebo-controlled study design.

Patients and Methods

Study design

This double-blind, randomised, placebo-controlled phase-III-study was performed in 10 study centres in Germany. The aim of the trial was to confirm the efficacy and tolerability of benfotiamine in the treatment of symptomatic diabetic polyneuropathy as well as the investigation of the dose-effectiveness relationship. The trial was performed in accordance with the Declaration of Helsinki, German law and GCP. The local ethics committees approved the trial and the patients gave their written informed consent.

Outcome measures, statistics and documentation

As primary endpoint of this study the NSS (Neuropathy Symptom Score) after 6 weeks was defined. A minimum of 180 patients (60 in each treatment group) was calculated to detect significant differences with $\Delta/\sigma = 1.5$, $\alpha = 5\%$ two-sided, power $1 - \beta = 90\%$. A difference in the main outcome parameter of at least 20% was expected.

Secondary outcome parameters were the improvement of NDS (Neuropathy Disability Score), TSS (Total Symptom Score according to Ziegler et al., 1995) and the vibration perception threshold (tuning fork test).

The results are given as mean of differences to baseline and the 95% confidence interval. Statistical differences were analysed with the Kruskal-Wallis H-test with a two-sided level of significance of 5%. For the ITT analysis, patients had to have at least outcome values after week 4. The results of the clinical findings and laboratory examinations were documented on standardised CRFs (case report forms) and entered in a data base. HbA_{1c} measurements (HPLC) were performed by the participating centres and a second control measurement was performed by a central laboratory according to a pre-defined method, which was part of the study protocol. The statistical analysis was performed with the statistic software SAS. Centre effects were not analysed.

Patients, randomisation, treatment and observation periods

A total of 181 male and female patients with type 1 or type 2 diabetes mellitus were screened for inclusion into the study. The main inclusion criterion was diagnosis of symmetrical distal diabetic polyneuropathy for at least 3 months scored by the NSS and NDS according to Young (1993) ≥ 5 . Other inclusion criteria were $\text{HbA}_{1c} \leq 9.5\%$, age 18–70 years and stable symptoms (≤ 1 point variation of NSS and of NDS between screening visit and start of study therapy). Key exclusion criteria were history of polyneuropathy for longer than 2 years, vitamin substitution (vitamins B, E and B-complex) within the preceding 4 weeks, continuation of neuropathy treatment with alpha-lipoic acid and other neuropathy medication (antidepressants, neuroleptics, tranquillisers, carbamazepine), preceding long-term treatment with psychotropic drugs for 3 months, and necessity of strong acting analgesics (opioids).

After screening, 165 patients were randomised to three treatment groups entering the wash-out phase: benfotiamine 3×200 mg ($n = 57$, group A), benfotiamine 3×100 mg ($n = 55$, group B) or placebo ($n = 53$, group C). The screening phase took 2 weeks, followed by a washout phase of 2 weeks with the daily application of 3×1 placebo. Study medication was prepared according to a randomisation list stratified for each centre. Each centre allocated a patient meeting the inclusion-/exclusion criteria to the lowest patient number available on the centre list. Study medication, i.e. tablets containing either 100 mg or 200 mg benfotiamine or placebo, respectively, for 3x daily application was prepared by the same manufacturer and did not differ in shape, colour or odour.

Patients under stable analgesic treatment could continue this during the study. The medication had to be documented. For rescue medication of pain, temporary analgesic co-medication was allowed, e.g. paracetamol up to a daily dose of 5×500 mg. After start of study medication, visits were scheduled at weeks 2, 4 and 6.

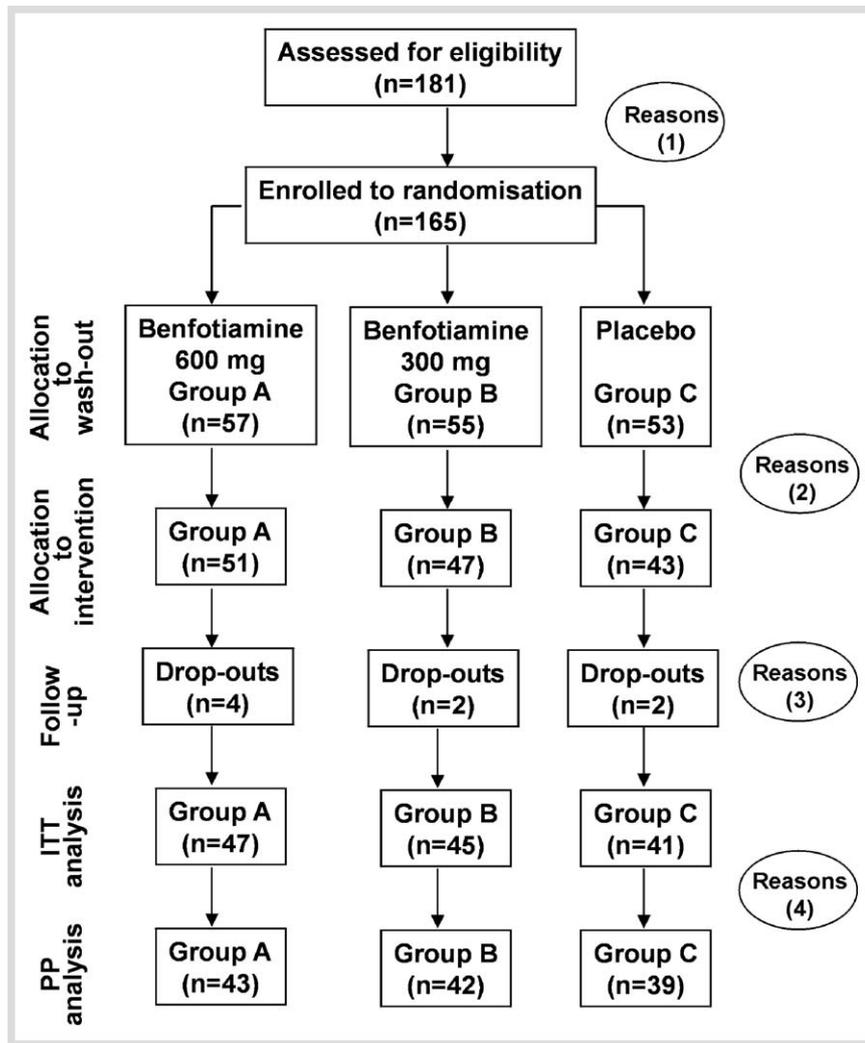


Fig. 1 Flow of participants through the study. ITT = intention to treat; PP = per protocol. Reasons (1): Non-compliance to inclusion-/exclusion criteria (n = 13); patient consent (n = 3). Reasons (2): Non-compliance with inclusion-/exclusion criteria: Prohibited comedication (n = 16), increased liver enzymes (n = 7); asymmetric polyneuropathy (n = 1). Reasons (3): Patients' demand (n = 4), in two cases because of undesired effects (Group A: impaired general condition and slight diarrhoea, group B: allergic reactions), non-compliance (n = 1), other complaints or diseases requiring (not allowed) comedication (n = 2), unknown (n = 1); totally 10 reasons for 8 patients. Reasons (4): LOCF excluded (n = 4), age not according to inclusion-/exclusion criteria (n = 4), new concomitant disease (n = 1).

Table 1 Demographic characteristics of the three treatment groups in the ITT (intention to treat) population and the PP (per protocol) population

Treatment group	ITT (n = 133)			PP (n = 124)		
	A (n = 47)	B (n = 45)	C (n = 41)	A (n = 43)	B (n = 42)	C (n = 39)
benfotiamine (daily dose)	600 mg	300 mg	placebo	600 mg	300 mg	placebo
mean age (years)	62	59	61	61	58	61
(minimum-maximum)	(47–73)	(46–72)	(42–72)	(47–71)	(46–69)	(42–70)
gender						
male	25	25	24	24	24	22
female	22	20	17	19	18	17
weight (kg)						
mean	87.8	86.5	85.6	88.9	85.0	85.9
(minimum-maximum)	(62–131)	(53–140)	(60–180)	(62–131)	(53–140)	(60–180)
height (cm) ^a						
mean	171.4	172.0	171.9	171.6	172.0	171.6
(minimum-maximum)	(155–189)	(155–192)	(149–188)	(155–189)	(155–192)	(149–188)
diabetes mellitus						
type 1	8	6	2	7	6	1
type 2	39	39	39	36	36	38
diabetes duration (years)						
mean	13.2	12.0	11.7	13.1	12.0	11.3
(minimum-maximum)	(0.75–41)	(0.25–51)	(0.5–37)	(0.75–41)	(0.25–51)	(0.5–37)
HbA _{1c}						
mean	7.8	7.7	7.6	7.8	7.7	7.6
(minimum-maximum)	(6.0–10.1)	(6.2–9.4)	(5.5–9.7)	(6.0–10.1)	(6.2–9.4)	(5.5–9.7)

Table 2 Baseline values of primary and secondary efficacy variables (mean, minimum-maximum)

Treatment group	ITT (n=133)			PP (n=124)		
	A (n=47)	B (n=45)	C (n=41)	A (n=43)	B (n=42)	C (n=39)
NSS (Neuropathy Symptom Score)	7.7 (5–9)	7.6 (5–9)	7.6 (5–9)	7.8 (5–9)	7.6 (5–9)	7.8 (5–9)
TSS (Total Symptom Score)	6.2 (1–14.64)	6.0 (0–14.64)	4.9 (0–13.98)	6.1 (1–14.64)	5.8 (0–14.64)	4.9 (0–13.98)
NDS (Neuropathy Disability Score)	7.6 (5–10)	8.3 (5–10)	7.9 (5–10)	7.6 (5–10)	8.3 (5–10)	7.9 (5–10)
Tuning fork test						
left side	3.4	3.0	3.5	3.4	2.9	3.4
right side	3.4	3.0	3.5	3.3	3.0	3.4

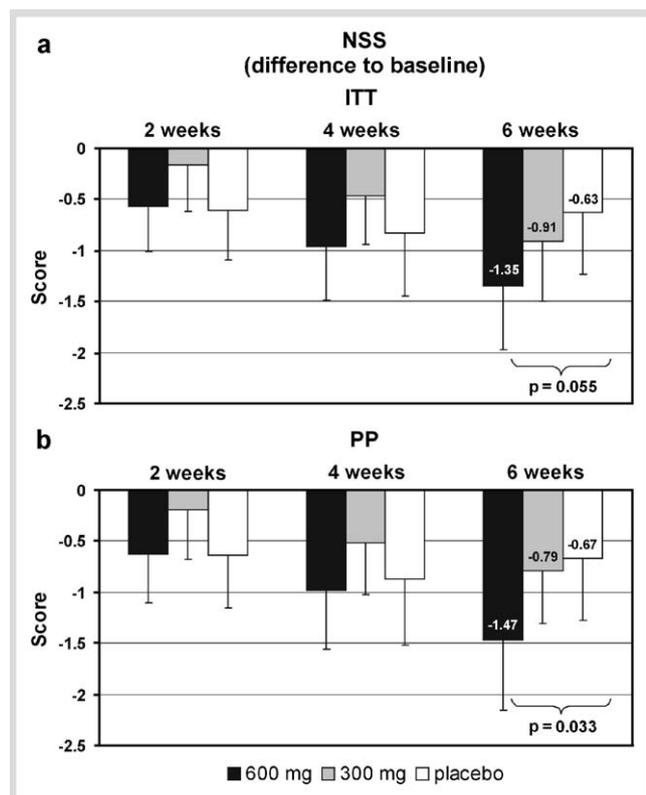


Fig. 2 Reduction of NSS (Neuropathy Symptom Score) under two different benfotiamine dosages (600 mg and 300 mg daily) and placebo. Each column represents mean of changes to baseline visit and its 95 % confidence interval. ITT = intention to treat (a), PP = per protocol (b). The difference is statistically slightly above significance level in the ITT population, but significant in the PP population.

Evaluation populations

All patients receiving at least one medication dose were included in the safety population. The assignment of the patients to the efficacy populations (ITT and PP) was performed by assessment of the inclusion/exclusion criteria, as well at screening or at the wash-out phase before start of active study medication (Fig. 1). Treatment duration had to be at least 4 weeks. For patient drop-outs before week 6, the LOCF method (Last Observation Carried Forward) was applied for the ITT analysis. Minor deviations from these and other criteria were assessed for clinical importance. In the assignment to the ITT population, the following minor protocol-deviations did not lead to an exclusion from the population: Minor or only temporary increase of HbA_{1c} up to 10.1%, age over 70 years. For definition of PP, age over 70 years and LOCF were exclusion criteria, furthermore new co-morbidities needing new co-medication.

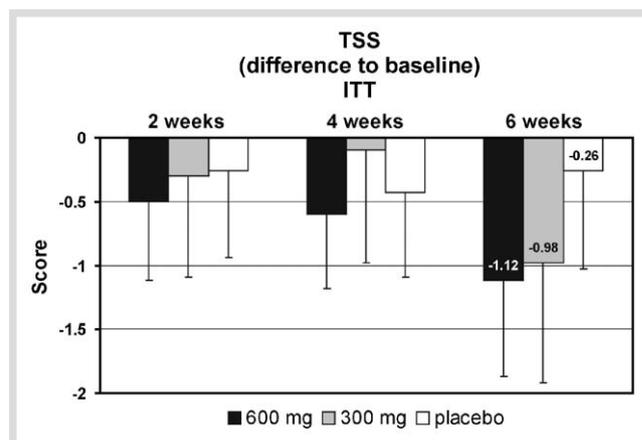


Fig. 3 Reduction of TSS (Total Symptom Score) under two different benfotiamine dosages (600 mg and 300 mg daily) and placebo in the ITT (intention to treat) population. Each column represents mean of changes to baseline visit and its 95 % confidence interval.

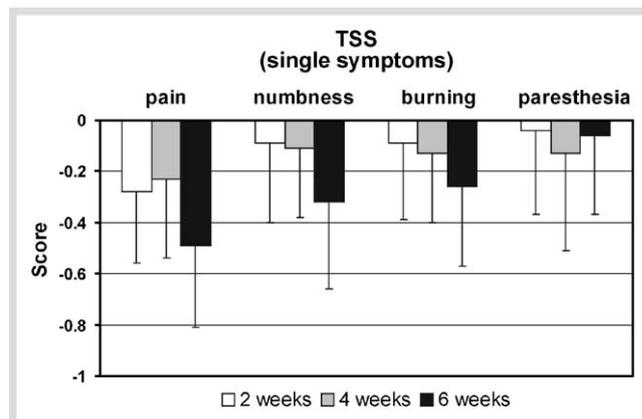


Fig. 4 Reduction of single symptoms of the TSS (Total Symptom Score) during treatment with 600 mg benfotiamine daily (group A) in the ITT (intention to treat) population. Each column represents mean of changes to baseline visit and its 95 % confidence interval.

Results

Demographic and basic clinical data

Demographic data were comparable in the three treatment groups (see Table 1). The mean age was approximately 60 years; there were more males than females (56 vs. 44%). The mean duration of diabetes mellitus was approximately 12 years, mostly type 2 (more than 85%). The mean HbA_{1c} was 7.7%. In accordance with the inclusion and exclusion criteria, the duration of diabetic neuropathy was between 3 months and 2 years. The baseline values of the efficacy parameters are summarised in Table 2 for the ITT and PP populations.

Primary efficacy outcome: Changes from baseline in NSS

At inclusion, the Neuropathy Symptom Score (NSS) was comparable in all three groups (see **Table 2**, median in all groups: 8). After 6 weeks of treatment, the improvement from baseline in NSS was greatest in group A (600 mg benfotiamine) and smallest in group C (placebo, **Fig. 2**). The difference between the groups was statistically significant ($p=0.033$) in the PP population. In the ITT population, the difference was slightly above significance level ($p=0.055$).

Secondary efficacy outcomes

TSS

In the Total Symptom Score (TSS), the improvement from baseline after 6 weeks of treatment was greatest in the 600 mg group and smallest under placebo, although the difference was not significant between the groups (**Fig. 3**). Observing the individual parameters of the TSS in group A (600 mg benfotiamine), the best improvement was found for the symptom “pain”, followed by “numbness”, “burning” and “paresthesia” (**Fig. 4**). In an open long-term extension of the study, the improvement in group A further increased.

NDS

The NDS (Neuropathy Disability Score) showed a tendency to increasing improvement with time. After 6 weeks, the score was decreased by 0.8–1.1 points (ITT). However, the baseline values differed between the groups from 7.6 (group A) to 8.3 (group B). There was no significant difference between the groups at any time ($p=0.609$ after 6 weeks in the ITT population).

Vibration threshold

In the tuning fork test, only minimal differences could be detected between the treatment groups. The mean baseline values differed between 2.9 and 3.5 and decreased by 0.18–0.40 (ITT) and 0.21–0.42 (PP) after 6 weeks, respectively.

Metabolic control

At inclusion, HbA_{1c} was comparable in the treatment groups: The means were 7.8% in group A (600 mg benfotiamine), 7.7% in group B (300 mg benfotiamine) and 7.6% in group C (placebo) and did not change significantly during the treatment duration of 6 weeks.

Safety

There were no clinically relevant changes during study treatment in fasting glucose and other laboratory values, blood pressure, heart rate or urine chemistry. Only a few treatment-related adverse events were reported during the study. In 6 patients, slight gastrointestinal disorders were recorded, skin/allergic reactions in 2 patients. Other adverse events were unspecific disorders like disturbed general well-being, tiredness, dizziness or deterioration of the baseline situation. In both benfotiamine groups, the number of patients with adverse events was comparable to placebo, demonstrating the good tolerability of a daily dose of 300 mg or 600 mg benfotiamine.

Discussion



In the BEDIP study (Haupt et al., 2005), a significant therapeutic effect of benfotiamine (400 mg daily) was observed using the score according to Katzenwadel. The present study demon-

strated 600 mg of benfotiamine showing greater efficacy than 300 mg in the NSS. The aim of this study, however, to confirm the results of the pilot study (Haupt et al., 2005), missed significance in the ITT population and was met only in the PP analysis. Whereas the ITT analysis is the more robust evaluation, the more investigational approach of the PP analysis by selection of patients according to the inclusion/exclusion criteria justify the conclusion, that significant treatment effects of benfotiamine could be proven also in an ITT population using an optimised study design. Especially the exclusion of LOCF in the PP population might explain the difference of significance between ITT and PP population, because during the first weeks a high placebo effect was observed, discriminating from the therapeutic effect only at 6 weeks. Though Haupt et al. (2005) showed a fast onset of action with significant results already after 3 weeks by the test of Katzenwadel, one has to take into account differences in the scores used for analysis. Depending on the parameters or symptoms tested with different scores, the onset of therapeutic improvement might need different time spans. As was shown by **Fig. 4**, the symptom “pain” seems to be influenced best by benfotiamine, whereas “paresthesia” showed nearly no effect after 6 weeks even under the higher benfotiamine dose. As a consequence, the definition of the primary endpoint has to be considered thoroughly in dependence of treatment duration or vice versa.

Furthermore, it was difficult to estimate the magnitude of an effect on the NSS and to compute the sample size for this study, because this score had not been used for documentation of treatment effects so far but rather for epidemiological purposes. The NSS decreased by 1.35 points (17%) under 600 mg benfotiamine and only by 8.3% under placebo (ITT population) after 6 weeks. Assuming that these differences are due to reduction of symptoms, this means e.g. complete relieve of at least one symptom of neuropathy, a clinically meaningful result. On the other hand, for sample size calculation a difference of at least 20% had been expected, leading to inappropriate sample size. Furthermore, the study population corresponded to sample size calculation only during the screening phase. Thereafter, reduced patient numbers decreased the power of the study considerably. This might contribute to missing statistical significance in the ITT analysis additional to the problem of LOCF.

Comparing the characterisation of the disease and the symptoms by the different scores, a discrepancy at baseline can be seen. Whereas the severity of deficits evaluated by the NDS and the severity of symptoms evaluated by the NSS were moderate to severe, TSS indicates only mild symptoms/pain in mean, with a broad variation in all treatment groups between minimum and maximum at baseline. Thus, it is possible that although the symptoms were typical and severe for diabetic polyneuropathy according to the NSS, severity and frequency of evaluated symptoms were relatively low according to the TSS in a part of the patients. With mean baseline values of TSS between 4.9–6.2 points, reduction by benfotiamine was 18% (600 mg), corresponding to more than one point, compared to only 5.3% under placebo, i.e. a relative difference in favour of benfotiamine of 12.7%. A reduction of one point of TSS means, that e.g. the severity of one symptom changes from moderate to mild or from severe to moderate, a clinically relevant result, especially considering the aspect that the symptom “pain” seems to be best influenced by benfotiamine (**Fig. 4**). In the SYDNEY 2 trial (Ziegler et al., 2006), oral treatment of patients suffering from diabetic polyneuropathy with different doses of alpha-lipoic

acid (600, 1.200 and 1.800mg daily compared to placebo) for 5 weeks showed a relative difference in favour of alpha-lipoic acid between 16–20% for the TSS, which was defined as primary endpoint with considerably less baseline differences and higher initial values compared to the BENDIP study.

As a pathogenetically based treatment, benfotiamine was expected also to improve NDS or at least slow progression. A tendency to improvement was found in all groups with a high placebo effect leading to non-significant differences between the groups. For demonstrating a slowing of progression however, the treatment duration of 6 weeks was too short.

In conclusion, this study may be the basis for a following trial using another primary endpoint, e.g. the TSS or NTSS-6 (Basty et al., 2005), alternatively a numerical pain rating scale with a precise definition of severity of the disease at inclusion based on these scores. This definition should avoid mild disease, because a high placebo effect will mask the therapeutic effect, and severe disease, because a point of no return by irreversible degeneration of nerve tissue (Cellek, 2004) would impede therapeutic improvements. Additionally, the type of diabetes might play a role in pathogenesis of diabetic complications (Kasalova et al., 2006), with consequences of therapeutic interventions, or the quality of blood glucose control (Arora et al., 2006). If the promising results could be confirmed in another controlled clinical study under optimised conditions, benfotiamine would offer a therapy of diabetic neuropathy, which is well substantiated by the pharmacodynamic profile of benfotiamine (Hammes et al., 2003). As the general pathological basis of all changes in metabolism caused by enhanced glucose levels is the production of superoxide by the mitochondrial electron-transport chain (Brownlee, 2001), benfotiamine is a pathogenetically based, causal treatment option with a broader mechanism of action as other inhibitors of AGE production (aminoguanidine, pimagendine), which proved to be beneficial in animal experiments (Kihara et al., 1991) but without clinical proof of efficacy in diabetic complications so far (Bolton et al., 2004; Freedman et al., 1999). Based on the data of Thornalley et al. (2007), a thiamine deficiency is to be expected in diabetic patients even if masked in conventional measurements, justifying a probative application of benfotiamine in patients with neuropathy.

Acknowledgements

▼ We thank following study centres for contributing patient results for this study: H. Kruthaup, Papenburg; H. Schmechel, Erfurt; R. Zick, Lingen (Ems); K.J. Ruhnau, Berlin; J. Schwinn, Stuttgart; G. Willms, Leverkusen; B. Schulze-Schleppinghoff, Essen.

Conflict of interest: H. Stracke received a fee for speaking, W. Gaus and K. Federlin for consulting, U. Achenbach is employed by Wörwag Pharma GmbH, the manufacturer of benfotiamine.

References

- Arora S, Lidor A, Abularrage CJ, Weiswasser JM, Nylen E, Kellcut D, Sidawy AN. Thiamine (vitamin B1) improves endothelium-dependent vasodilation in the presence of hyperglycemia. *Ann Vasc Surg* 2006; 20 (5): 653–658
- Basty 3rd EJ, Price KL, Bril V, the MBBQ Study Group. Development and validity testing of the neuropathy total symptom score-6: questionnaire for the study of sensory symptoms of diabetic peripheral neuropathy. *Clin Ther* 2005; 27 (8): 1278–1294
- Bolton WK, Cattran DC, Williams ME, Adler SG, Appel GB, Cartwright K, Foiles PG, Freedman BI, Raskin P, Ratner RE, Spinowitz BS, Whittier FC, Wuerth JP, ACTION I Investigator Group. Randomized trial of an inhibitor of formation of advanced glycation end products in diabetic nephropathy. *Am J Nephrol* 2004; 24 (1): 32–40
- Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; 414: 813–820
- Cellek S. Point of no return for nitrenergic nerves in diabetes: a new insight into diabetic complications. *Curr Pharm Des* 2004; 10 (29): 3683–3695
- Freedman BI, Wuerth JP, Cartwright K, Bain RP, Dippe S, Hershon K, Mooradian AD, Spinowitz BS. Design and baseline characteristics for the aminoguanidine Clinical Trial in Overt Type 2 Diabetic Nephropathy (ACTION II). *Control Clin Trials* 1999; 20 (5): 493–510
- Hammes HP, Du X, Edelstein D, Taguchi T, Matsumura T, Ju Q, Lin J, Bierhaus A, Nawroth P, Hannak D, Neumaier M, Bergfeld R, Giardino I, Brownlee M. Benfotiamine blocks three major pathways of hyperglycaemic damage and prevents experimental diabetic retinopathy. *Nature Medicine* 2003; 9 (3): 294–299
- Haslbeck KM, Schleicher E, Bierhaus A, Nawroth P, Haslbeck M, Neundörfer B, Heuss D. The AGE/RAGE/NF- κ B pathway may contribute to the pathogenesis of polyneuropathy in impaired glucose tolerance (IGT). *Exp Clin Endocrinol Diabetes* 2005; 113: 288–291
- Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic polyneuropathy – a three-week randomized, controlled pilot study (BEDIP study). *Int J Clin Pharmacol Ther* 2005; 43: 71–77
- Herholz H. Costs of diabetes: Complications are expensive. *Diabetes Stoffwechsel Herz* 2006; (Suppl 1): 7–11
- Kasalova Z, Prazny M, Skrha J. Relationship between peripheral diabetic neuropathy and microvascular reactivity in patients with type 1 and type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2006; 114: 52–57
- Kihara M, Schmelzer JD, Poduslo JF, Curran GL, Nickander KK, Low PA. Aminoguanidine effects on nerve blood flow, vascular permeability, electrophysiology, and oxygen free radicals. *Proc Natl Acad Sci* 1991; 88: 6107–6111
- Ledermann H, Wiedey KD. Behandlung der manifesten diabetischen Polyneuropathie. Therapeutische Wirkung des neurotrophen Vitamin-B-Komplexes B1-B6-B12. *Therapiewoche* 1989; 39: 1445–1449
- Schmidt J. Wirksamkeit von Benfotiamin bei diabetischer Neuropathie. Breite Anwendungsbeobachtung unterstreicht Praxisbenefit. *Kassenarzt* 2002; 14/15: 40–43
- Stirban A, Negrean M, Stratmann B, Gawlowski T, Horstmann T, Gotting C, Kleesiek K, Mueller-Roesel M, Koschinsky T, Uribarri J, Vlassara H, Tschöepe D. Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advanced glycation end products in individuals with type 2 diabetes. *Diabetes Care* 2006; 29 (9): 2064–2071
- Stracke H, Lindemann A, Federlin K. A benfotiamine-vitamin B combination in treatment of diabetic polyneuropathy. *Exp Clin Endocrinol Diab* 1996; 104: 311–316
- Tesfaye S, Stevens LK, Stephenson JM, Fuller JH, Plater M, Ionescu-Tirgoviste C, Nuber A, Pozza G, Ward JD, EURODIAB IDDM Study Group. Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM complications study. *Diabetologia* 1996; 39: 1377–1384
- Thornalley PJ, Babaei-Jadidi R, Al Ali H, Rabbani N, Antonysunil A, Larkin J, Ahmed A, Rayman G, Bodmer CW. High prevalence of low plasma thiamine concentration in diabetes linked to a marker of vascular disease. *Diabetologia* 2007; 50: 2164–2170
- Winkler G, Pal B, Nagybeganyi E, Öry I, Poochnavec M, Kempler P. Effectiveness of different benfotiamine dosage regimens in the treatment of painful diabetic neuropathy. *Drug Res* 1999; 49 (1): 220–224
- Woelk H, Lehl S, Bitsch R, Koepcke W. Benfotiamine in treatment of alcoholic polyneuropathy: An 8 week randomized controlled study (BAP I study). *Alcohol Alcoholism* 1998; 33: 631–638
- Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia* 1993; 36: 150–154
- Ziegler D, Hanefeld M, Ruhnau KJ, Meissner HP, Lobisch M, Schutte K, Gries FA. Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant α -lipoic acid. *Diabetologia* 1995; 38: 1425–1433
- Ziegler D, Ametov A, Barinova A, Dyck PJ, Gurieva I, Low PA, Munzel U, Yakhno N, Raz I, Novosadova M, Maus J, Samigullin R. Oral treatment with α -lipoic acid improves symptomatic diabetic polyneuropathy. The SYDNEY 2 trial. *Diabetes Care* 2006; 29: 2365–2370
- Ziegler D, Bierhaus A. Treatment of diabetic neuropathy. *Dtsch Med Wochenschr* 2007; 132: 1043–1047