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Effects of 3-week oral treatment with the antioxidant thioctic acid (α-lipoic acid) in symptomatic diabetic polyneuropathy

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Abstract

Aims To evaluate the efficacy and safety of short-term oral treatment with the antioxidant thioctic acid (TA) on neuropathic symptoms and deficits in patients with Type 2 diabetes mellitus with symptomatic polyneuropathy.

Methods Patients were randomly assigned to oral treatment with 600 mg of TA *t.i.d.* ($n = 12$) or placebo ($n = 12$) for 3 weeks. Neuropathic symptoms (pain, burning, paraesthesiae, and numbness) in the feet were scored at weekly intervals and summarized as a Total Symptom Score (TSS). The Hamburg Pain Adjective List (HPAL) and the Neuropathy Disability Score (NDS) were assessed at baseline and day 19.

Results At baseline the TSS, HPAL, and NDS were not significantly different between the groups. The TSS in the foot decreased from baseline to day 19 by -3.75 ± 1.88 points (–47%) in the TA group and by -1.94 ± 1.50 points (–24%) in the placebo group ($P = 0.021$ for TA vs. placebo). The total HPAL score decreased from baseline to day 19 by -2.20 ± 1.65 points (–60%) in the TA group and by -0.96 ± 1.32 points (–29%) in the placebo group ($P = 0.072$ for TA vs. placebo). The NDS decreased by -0.27 ± 0.47 points in the TA group, whereas it slightly increased by $+0.18 \pm 0.4$ points in the placebo group ($P = 0.025$ for TA vs. placebo). No differences between the groups were noted regarding the rates of adverse events.

Conclusions These preliminary findings indicate that oral treatment with 600 mg of TA *t.i.d.* for 3 weeks may improve symptoms and deficits resulting from polyneuropathy in Type 2 diabetic patients, without causing significant adverse reactions.

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Keywords antioxidants, diabetic polyneuropathy, Neuropathy Disability Score, thioctic acid, Total Symptom Score

Abbreviations GGT, gamma-glutamyl transpeptidase; HPAL, Hamburg Pain Adjective List; NDS, Neuropathy Disability Score; SGOT (AST), aspartate aminotransferase; SGPT (ALT), alanine aminotransferase; TA, thioctic acid; TSS, Total Symptom Score

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Introduction

There is now general agreement that near-normoglycaemia can prevent chronic diabetic complications, including polyneuropathy, in both Type 1 and Type 2 diabetic patients [1,2]. However, since near-normal glycaemic control is achievable in only a limited number of patients, alternative therapeutic approaches are desirable to treat diabetic polyneuropathy. In recent years, tentative therapeutic approaches have been developed to interfere with the pathogenesis of diabetic polyneuropathy. One of these therapeutic interventions includes the reduction of free radical-mediated oxidative stress by antioxidants such as thioctic acid (TA) [3,4]. Three weeks of parenteral treatment with 600 mg of TA reduced the symptoms of diabetic polyneuropathy in Type 2 diabetic patients [5]. However, the intravenous drug application is a time consuming procedure for the patients and limits the access to this therapy to the general diabetic population in practice. Pharmacokinetic studies have demonstrated that 1800 mg oral TA, using a novel oral formulation produce consistent blood levels comparable to those obtained with intravenous administration of 600 mg TA [6]. This study therefore aimed to evaluate whether the oral administration of 600 mg of TA *t.i.d.* using this formulation improves neuropathic symptoms and deficits.

Patients and methods

Study design and patients

This study (ORPIL: *Or*al *Pil*ot Study) was a randomized, double-blind, placebo-controlled monocentre trial using 1800 mg of TA (Thioctacid 600 HR®, ASTA Medica AG, Frankfurt am Main, Germany) or placebo in Type 2 diabetic outpatients with polyneuropathy, who were recruited from the Berlin Diabetes Academy unit. The oral 600 mg formulation of TA *t.i.d.* or placebo *t.i.d.* were administered for 19 days.

Ethical approval was obtained from the regional ethics committee and patients gave written informed consent. Entry criteria included age between 18 and 70 years, Type 2 diabetes treated with diet, oral anti-diabetic agents and/or insulin,

Table 1 Clinical data and outcome measures at entry with their changes during the study

	Placebo	Thioctic acid (TA)	*P*-value TA vs. placebo
Clinical characteristics			
Sex (m/f)	6/6	6/6	
Age (years)	62.1 ± 4.5	60.5 ± 6.9	0.53
Body mass index (kg/m^2)	28.5 ± 3.9	29.6 ± 4.0	0.52
Systolic blood pressure (mmHg)	142.0 ± 9.4	138.7 ± 12.8	0.50
Diastolic blood pressure (mmHg)	78.3 ± 8.0	82.0 ± 8.1	0.29
Duration of diabetes (years)	12.4 ± 10.9	10.6 ± 3.3	0.61
Duration of neuropathy (years)	3.8 ± 1.9	4.1 ± 1.4	0.68
Insulin treatment	11	12	
HbA_{1C} (%)	7.1 ± 1.8	7.7 ± 1.3	0.38
Total Symptom Score (TSS: feet)	(*n* = 11)	(*n* = 11)	
Baseline	8.18 ± 0.89	7.99 ± 0.97	0.64
Change day 19 vs. baseline	−1.94 ± 1.50	−3.75 ± 1.88	0.021
Subscore *paraesthesiae*	(*n* = 11)	(*n* = 11)	
Baseline	2.00 ± 0.74	1.91 ± 0.57	0.75
Change day 19 vs. baseline	−0.51 ± 0.98	−0.82 ± 0.60	0.517
Subscore *burning*	(*n* = 11)	(*n* = 11)	
Baseline	2.11 ± 0.48	2.03 ± 0.50	0.71
Change day 19 vs. baseline	−0.64 ± 0.59	−1.42 ± 0.75	0.012
Subscore *pain*	(*n* = 11)	(*n* = 11)	
Baseline	1.47 ± 0.54	1.69 ± 0.58	0.37
Change day 19 vs. baseline	0.79 ± 0.81	−1.39 ± 0.84	0.099
Subscore *numbness*	(*n* = 11)	(*n* = 11)	
Baseline	2.61 ± 0.13	2.36 ± 0.50	0.12
Change day 19 vs. baseline	0.00 ± 0.00	−0.12 ± 0.92	0.670
Hamburg Pain Adjective List (HPAL)	(*n* = 11)	(*n* = 10)	
Baseline	3.60 ± 0.72	3.74 ± 0.66	0.64
Change	−0.96 ± 1.32	−2.20 ± 1.65	0.072
Neuropathy Disability Score (NDS)	(*n* = 11)	(*n* = 11)	
Baseline	8.17 ± 1.34	8.50 ± 1.17	0.54
Change day 19 vs. baseline	0.18 ± 0.40	−0.27 ± 0.47	0.025

Values are mean ± SD or *n*.

evidence of distal symmetrical polyneuropathy (reduced/absent ankle reflexes, reduced vibration, thermal, tactile, pin-prick, and/or position sensation) with at least moderate severity of one or more of the typical symptoms (pain, burning, paraesthesiae, numbness) in the feet, equivalent to 4 or more points in the total symptom score. Exclusion criteria were identical with those used in the ALADIN Study [5].

Methods

Outcome measures

At baseline (day 1) and each subsequent visit neuropathic symptoms (pain, burning, paresthesiae, and numbness) were scored for severity by the physician. The Total Symptom Score (TSS) was used as a primary outcome measure as described previously [5]. The intra-individual coefficient of variation for the TSS determined on two separate days within one week in Type 2 diabetic patients with symptomatic polyneuropathy ($n = 315$; age 57.0 ± 6.9 years) was 22%. The Neuropathy Disability Score (NDS) was performed according to Young *et al.* [7] The Hamburg Pain Adjective List (HPAL), a validated multidimensional specific pain questionnaire that is reliable and sensitive to changes in pain severity and quality in response to pain treatment [8], was filled out by the patient at baseline and on day 19 as described previously [5].

Laboratory methods

Glycosylated haemoglobin (HbA_{1c}) was measured at baseline and at day 19 as described previously [5]. Safety parameters including creatinine, haemoglobin, SGOT (aspartate aminotransferase), SGPT (alanine aminotransferase), GGT (gamma-glutamyl transferase), alkaline phosphatase, erythrocyte sedimentation rate, leucocytes, platelets, total bilirubin, uric acid, cholesterol, and triglycerides were also determined at baseline and at day 19.

Statistical analyses

Continuous variables were given by the mean ± SD. The two-sided Student's *t*-test for independent samples was used for analysis of the changes from baseline to follow-up between the groups. Categoric variables were analysed by Fisher's exact test. All tests are of descriptive character only and therefore no α-adjustment was performed. The level of significance was set at $\alpha = 0.05$. Adverse events were coded according to the WHO/BfArM (Adverse Reaction Terminology) thesaurus.

Results

One patient on TA dropped out of treatment after 17 days owing to a lack of efficacy, and one patient receiving placebo was withdrawn as a result of myocardial infarction. There were no other adverse events reported. There were no significant differences between the groups regarding the clinical characteristics at entry (Table 1) and the laboratory and safety parameters at entry and during the study. The TDS indicated a moderate to severe degree of neuropathic deficits on average. The TSS, HPAL, and NDS did not differ significantly between the groups at baseline. The TSS in the feet decreased from baseline to day 19 by 47% in the TA group and by 24% in placebo ($P = 0.021$). When an intention-to-treat analysis was applied, the TSS decreased by -3.61 ± 1.61 and -1.83 ± 1.47 points, respectively, $P = 0.017$. Regarding the individual symptoms a significant difference between TA and placebo was detected for burning ($P = 0.012$). The reduction of pain intensity in the HPAL was higher in the TA group (–60%) than in placebo (–29%), but this difference reached only borderline significance ($P = 0.072$). The NDS decreased significantly in the TA group as compared with placebo ($P = 0.025$) (Table 1).

Conclusions

The findings of this randomized, double-blind placebo-controlled pilot study in Type 2 diabetic patients with symptomatic polyneuropathy indicate that short-term treatment over 3 weeks using a dose of 1800 mg of thioctic acid (TA) may ameliorate neuropathic symptoms as assessed by the TSS as well as deficits as scored by the NDS and this is not associated with significant adverse effects. These results are compatible with those of a previous trial demonstrating an improvement in the TSS after i.v. treatment with TA using a dose of 600 mg/day and improvement in the NDS using a dose of 1200 mg/day for 3 weeks [5]. The mechanisms of such a rapid improvement are unknown, but may be related to an increase in nerve blood flow mediated by the antioxidant action of the drug [3,9]. The preliminary results of this pilot study need to be confirmed in a longer-term multi-centre trial including an adequate sample size.

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