The Effects of Long-Term Oral Benfotiamine Supplementation on Peripheral Nerve Function and Inflammatory Markers in Patients With Type 1 Diabetes

A 24-month, double-blind, randomized, placebo-controlled trial

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OBJECTIVE—To study the effects of long-term oral benfotiamine supplementation on peripheral nerve function and soluble inflammatory markers in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS—The study randomly assigned 67 patients with type 1 diabetes to receive 24-month benfotiamine (300 mg/day) or placebo supplementation. Peripheral nerve function and levels of soluble inflammatory variables were assessed at baseline and at 24 months.

RESULTS—Fifty-nine patients completed the study. Marked increases in whole-blood concentrations of thiamine and thiamine diphosphate were found in the benfotiamine group (both $P < 0.001$ vs. placebo). However, no significant differences in changes in peripheral nerve function or soluble inflammatory biomarkers were observed between the groups.

CONCLUSIONS—Our findings suggest that high-dose benfotiamine (300 mg/day) supplementation over 24 months has no significant effects upon peripheral nerve function or soluble markers of inflammation in patients with type 1 diabetes.

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Benfotiamine, a synthetic thiamine monophosphate analog with improved bioavailability compared with thiamine (1), has been shown to prevent the development of microvascular complications in rats without changes in glycemic control (2). Short-term studies (3–12 weeks) in humans have suggested that high-dose benfotiamine (up to 600 mg/day) can improve symptomatic scores in diabetic polyneuropathy (3–5). To assess the efficacy of long-term supplementation, we conducted a 24-month, randomized, double-blind, placebo-controlled study of the effects of 300 mg/day benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

The study recruited 67 individuals with type 1 diabetes during routine appointments at the Norwegian Diabetic Centre. Inclusion criteria were *1*) age 18 to 60 years (inclusive), *2*) type 1 diabetes (>15-year duration), and *3*) normo- or microalbuminuria. All patients provided written informed consent. The study, which was approved by the regional ethics committee and the Norwegian Medicines Agency, was conducted as a parallel, randomized, double-blind, placebo-controlled prospective trial of 24-month duration. Patients in the active group were given 300 mg benfotiamine per day (Benfogamma, Wörwag Pharma GmbH).

We selected patients with type 1 diabetes of >15-year duration (mean 31-year duration) because we previously showed that these patients have reduced nerve conduction velocity (NCV) even if they do not have marked clinical neuropathy (6). Nerve conduction studies (NCS) were performed with Keypoint machines (Medtronic, Denmark) using surface electrodes with >45-min acclimatization (room temperature 22–24°C). Examinations were performed by one of three neurophysiologists. Abnormal NCS were defined as one or more abnormal Z score in two or more nerves, based on sural nerve amplitude (antidromic stimulation), tibial and peroneal NCV, tibial amplitude, increased F-wave minimum latency (F-min), and absent F-waves (only considered abnormal in tibial nerve). F-wave persistence (*N* F-waves/*N* of stimuli) was based on 20 consecutive stimulations. Heart-rate response to deep breathing (6 breaths/min; supine position) relative to the mean heart rate during the same minute and the immediate heart-rate response to standing (30:15 ratio) was also calculated.

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For clinical assessments, peripheral neuropathy was assessed by the diabetic neuropathy symptom score (DNS) (7) and the neuropathy disability score (NDS) (8). This included examination of the ankle reflex, vibration sensation using a 128-Hz tuning fork, and pinprick sensation of the great toe. We assessed cutaneous pressure perception using a 10-g Semmes-Weinstein monofilament at four validated plantar sites.

Blood samples were drawn after an overnight fast (0800 and 1000 h), prepared within 1 h, and kept frozen at −80°C for batch analysis (except thiamine derivatives and routine analyses).

Table 1—*Changes from baseline to 24 months in the placebo and benfotiamine group (per-protocol analysis)*

	Placebo $n = 31$	Benfotiamine $n = 28$	P Placebo	P Benfotiamine	P*
BMI (kg/m^2)	0.2 (1.1)	0.3 (1.4)	NS	NS	NS
Blood pressure (mmHg)					
Systolic	−4.5 (13.4)	1.0 (10.7)	NS	NS	NS
Diastolic	−0.6 (8.6)	6.5 (11.0)	NS	0.005	0.01
Albumin excretion (μg/min)	1.0 (−0.5 to 2.5)	0.0 (−1.0 to 10.0)	NS	NS	NS
Skin autofluorescence (arbitrary units)	0.2 (0.0–0.3)	0.1 (−0.3 to 0.5)	NS	NS	NS
Thiamine (ng/mL)	−0.2 (−5.1 to 4.2)	454.0 (112.0–897.1)	NS	<0.001	<0.001
Thiamine diphosphate (ng/mL)	−7.2 (22.1)	210.3 (77.3)	NS	<0.001	<0.001
Fibrinogen (g/L)	−0.1 (0.7)	0.1 (0.6)	NS	NS	NS
Serum creatinine (μmol/L)	−2.0 (−5.0 to 1.0)	0.5 (−5.3 to 5.3)	NS	NS	NS
Hemoglobin (g/100 mL)	0.1 (0.9)	0.2 (0.7)	NS	NS	NS
Hematocrit (fraction)	0.01 (0.03)	0.02 (0.02)	0.01	0.001	NS
Serum folate (nmol/L)	3.2 (−2.1 to 8.1)	−0.7 (−3.9 to 2.9)	0.01	NS	0.01
Homocysteine (μmol/L)	0.3 (1.8)	0.6 (1.8)	NS	NS	NS
HbA_{1c} %	0.50 (−0.23 to 0.70)	0.45 (0.18–0.73)	0.02	0.01	NS
White blood cells (×10^9/L)	0.0 (−0.9 to 0.8)	0.3 (−0.4 to 0.7)	NS	NS	NS
Cholesterol (mmol/L)	0.01 (0.78)	−0.14 (0.81)	NS	NS	NS
HDL (mmol/L)	−0.07 (0.39)	0.02 (0.32)	NS	NS	NS
Triglycerides (mmol/L)	0.00 (0.43)	0.04 (0.38)	NS	NS	NS
Nerve-conduction variables					
Peroneal nerve					
Amplitude (mV)	−0.2 (−1.5 to 0.7)	−0.5 (−1.6 to 0.8)	NS	0.002	NS
Conduction velocity (m/s)	−0.1 (−2.3 to 2.0)	−1.2 (−3.9 to 2.0)	NS	NS	NS
F-wave persistence (%)	0.0 (−27.5 to 7.5)	−12.5 (−30.0 to 3.8)	NS	0.04	NS
F-wave min latency (ms)	0.2 (−2.2 to 1.1)	0.5 (−1.2 to 1.9)	NS	NS	NS
Tibial nerve					
Amplitude (mV)	−0.2 (−1.6 to 2.1)	0.1 (−0.5 to 1.1)	NS	NS	NS
Conduction velocity (m/s)	0.4 (−2.4 to 2.3)	−1.2 (−3.6 to 1.5)	NS	NS	NS
F-wave persistence (%)	0.0 (−2.5 to 0.0)	0.0 (−12.5 to 0.0)	NS	0.03	NS
F-wave min latency (ms)	−0.3 (−1.6 to 2.8)	−0.3 (−3.7 to 1.6)	NS	NS	NS
Sural nerve					
Amplitude (μV)	0.0 (−2.3 to 1.2)	0.0 (−1.4 to 1.9)	NS	NS	NS
Conduction velocity (m/s)	−3.3 (−10.7 to 0.0)	−1.1 (−5.3 to 1.0)	0.003	NS	NS
Heart rate					
Deep breathing (%)	−0.5 (−6.3 to 5.9)	−2.0 (−8.4 to 2.0)	NS	NS	NS
Response to standing (30:15 ratio)	−0.04 (−0.13 to 0.03)	−0.03 (−0.23 to 0.03)	NS	0.04	NS
Inflammatory variables					
E-selectin (ng/mL)	−2.8 (−8.0 to 0.7)	−1.5 (−12.9 to 4.6)	0.03	NS	NS
VCAM-1 (ng/mL)	−59.7 (−108.0 to 61.1)	−21.5 (−67.7 to 77.9)	NS	NS	NS
ICAM-1 (ng/mL)	1.2 (−31.2 to 22.6)	−7.9 (−33.3 to 26.3)	NS	NS	NS
P-selectin (ng/mL)	0.0 (−2.6 to 2.8)	−1.7 (−6.3 to 2.8)	NS	NS	NS
MCP-1 (pg/mL)	6.0 (−40.0 to 28.0)	2.0 (−25.5 to 18.0)	NS	NS	NS
Interleukin-6 (pg/mL)	−0.2 (−1.0 to 0.3)	0.0 (−0.3 to 1.0)	NS	NS	NS
TNF-α (pg/mL)	0.2 (−0.1 to 0.5)	0.5 (−0.5 to 1.2)	NS	NS	NS
CD40 L (pg/mL)	32.7 (12.4–62.8)	22.8 (−3.2 to 126.8)	<0.001	0.005	NS
C-reactive protein (mg/L)	−0.2 (−1.8 to 1.0)	−0.3 (−2.2 to 0.8)	NS	NS	NS
Interleukin-18 (pg/mL)	−3.8 (−40.5 to 12.6)	−17.9 (−45.4 to 8.2)	NS	0.03	NS
Oxidized LDL (units/L)	1.0 (−5.8 to 8.5)	1.9 (−3.3 to 4.0)	NS	NS	NS

Data are presented as means (SD) with P values of two independent samples t tests or as medians (Q1–Q3) with P values of Mann-Whitney U tests. ICAM, intracellular adhesion molecule; MCP, monocyte chemoattractant protein; TNF-α, tumor necrosis factor-α; VCAM, vascular cell adhesion molecule. *P values for the differences between the changes in placebo and benfotiamine groups.

Statistics

Means (95% CIs) are given for continuous normally distributed data and medians (quartiles) for highly skewed data. Differences between groups over 24 months were tested by two independent sample *t* tests or Mann-Whitney *U* tests. Power calculations based on our primary end point (peroneal NCV) indicated that at least 55 patients would be required (standardized difference 0.75; 80% power, 5% significance level). Changes from baseline to 24 months within each group were tested by paired *t* tests for normally distributed data; otherwise, Wilcoxon was used. Per-protocol data were used in the analysis. Analyses were performed with STATA/IC 11 and PASW Statistics for Windows.

RESULTS

Study completion and baseline characteristics

The study was completed by 59 of the 67 patients who were recruited. No significant differences were found between the benfotiamine and placebo groups in any biochemical or neurophysiologic variable at baseline (Supplementary Table 1). Of the 59 patients who completed the study, 56% had abnormal NCS (based on stringent neurophysiologic assessment), and 16% had probable diabetic sensorimotor polyneuropathy (clinical evaluation of both signs and symptoms) at baseline (Supplementary Table 1).

Changes from baseline within each group and between the randomized groups

Biochemical variables. No changes outside of the normal reference ranges were detected in safety parameters (data not shown). We found a marked increase in thiamine and thiamine diphosphate in all patients who received benfotiamine (Table 1, both $P < 0.001$). Diastolic blood pressure (DBP) was also significantly increased in the benfotiamine group ($P < 0.01$) and was significantly different from the change in the placebo group ($P < 0.05$). We found a significant increase in serum folate in the placebo group ($P < 0.05$), which was significantly different from the change in the benfotiamine group ($P < 0.05$).

Nerve conduction variables. No significant differences were noted in changes between the groups for peroneal NCV or any other nerve conduction parameter (Table 1). Peroneal nerve F-wave persistence ($P < 0.05$) and amplitude ($P = 0.01$) as well as tibial nerve F-wave persistence ($P < 0.05$) were significantly reduced in the benfotiamine group. Sural NCV was significantly reduced ($P < 0.05$) in the placebo group. Whereas 56% of all patients had abnormal NCS at baseline, 64% had abnormal scores at 24 months (four patients in the benfotiamine and one in the placebo group went from normal to abnormal NCS, data not shown).

Soluble inflammatory markers. There were no significant differences in changes between the groups in any of the inflammatory markers (Table 1).

CONCLUSIONS

—Peroneal F-wave persistence and amplitude in addition to tibial nerve F-wave persistence and heart-rate response to standing were significantly reduced in the benfotiamine group, which may indicate a slight deterioration of nerve function. However, we did not find any significant differences between the benfotiamine and placebo group. The difference between the current study and former studies that reported a positive effect of benfotiamine may be related to differences in the investigated populations. Symptomatic polyneuropathy was not an inclusion criterion in the current study (symptom scoring was not meaningful because most patients were asymptomatic). However, because the former studies did not report neurophysiologic function, we cannot exclude that the reported effect was related to symptom reduction and not improved nerve function per se. In support of this view, benfotiamine has been reported to have an antinociceptive effect in inflammatory and neuropathic pain models (9).

In conclusion, despite a marked improvement in thiamine status, long-term high-dose benfotiamine had no significant effect on peripheral nerve function or inflammatory markers in patients with type 1 diabetes.

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D.A.F. designed the study, performed non-neurologic clinical assessments, and wrote the manuscript. L.M.D. performed the statistical analysis and contributed to writing the manuscript. I.A.H. and K.B.N. performed the neurologic analyses and contributed to writing the manuscript. K.A.S. performed non-neurologic clinical assessments. I.S. performed blood sampling and analysis and contributed to writing the manuscript. K.F.H. designed the study, performed non-neurologic clinical assessments, and contributed to writing the manuscript. D.A.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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