

The Sensory Symptoms of Diabetic Polyneuropathy Are Improved With α -Lipoic Acid

The SYDNEY Trial

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several other neuropathic end points. This improvement of symptoms was attributed to improved nerve pathophysiology, not to increased nerve fiber degeneration. Because of its safety profile and its effect on positive neuropathic sensory symptoms and other neuropathic end points, this drug appears to be a useful ancillary treatment for the symptoms of diabetic polyneuropathy.

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OBJECTIVE — Because α -lipoic acid (ALA), a potent antioxidant, prevents or improves nerve conduction attributes, endoneurial blood flow, and nerve (Na(+)/K(+) ATPase activity in experimental diabetes and in humans and may improve positive neuropathic sensory symptoms, in this report we further assess the safety and efficacy of ALA on the Total Symptom Score (TSS), a measure of positive neuropathic sensory symptoms.

RESEARCH DESIGN AND METHODS — Metabolically stable diabetic patients with symptomatic (stage 2) diabetic sensorimotor polyneuropathy (DSPN) were randomized to a parallel, double-blind study of ALA (600 mg) ($n = 60$) or placebo ($n = 60$) infused daily intravenously for 5 days/week for 14 treatments. The primary end point was change of the sum score of daily assessments of severity and duration of TSS. Secondary end points were sum scores of neuropathy signs (NIS), symptoms (NSC), attributes of nerve conduction, quantitative sensation tests (QSTs), and an autonomic test.

RESULTS — At randomization, the groups were not significantly different by the criteria of metabolic control or neuropathic end points. After 14 treatments, the TSS of the ALA group had improved from baseline by an average of 5.7 points and the placebo group by an average of 1.8 points ($P < 0.001$). Statistically significant improvement from baseline of the ALA, as compared with the placebo group, was also found for each item of the TSS (lancinating and burning pain, asleep numbness and prickling), NIS, one attribute of nerve conduction, and global assessment of efficacy.

CONCLUSIONS — Intravenous racemic ALA, a potent antioxidant, rapidly and to a significant and meaningful degree, improved such positive neuropathic sensory symptoms as pain and

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Abbreviations: ALA, α -lipoic acid; DSPN, diabetic sensorimotor polyneuropathy; HP-DB, heart pulse deep breathing; ITT, intent-to-treat; NIS, neuropathy impairment score; NIS(LL), NIS of lower limbs; NSC, neuropathy symptoms and change; NSC(LL), neuropathy symptoms and change of lower limbs; PP, per protocol; QST, quantitative sensation test; TSS, Total Symptom Score.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The neuropathies associated with diabetes are heterogeneous (1). Perhaps the most common variety is diabetic sensorimotor polyneuropathy (DSPN), the disorder studied here. This variety appears to be caused by chronic hyperglycemia and associated metabolic derangements, damaging neurons (axons) or Schwann cells (or myelin) directly or indirectly by functional and structural alterations of microvessels or the blood nerve barrier. Inflammation, perhaps from immune mechanisms, may also be implicated in some cases (2).

Recognizing that total hyperglycemic exposure may be the most important modifiable risk covariate for diabetic complications such as DSPN (3–8), why search for ancillary treatments in addition to rigorous glucose control? First, despite considerable effort to achieve near euglycemia (by frequent monitoring of plasma glucose, use of multiple injections of insulin, or use of insulin pumps), many diabetic patients cannot, or will not, achieve the desired level of metabolic control (3,8). Such patients might benefit from ancillary treatments. Second, the mechanisms underlying positive neuropathic sensory symptoms may be different or overlapping from ones relating to neuropathic impairment (9). Among the ancillary therapies considered are aldose reductase inhibitors (10), *myo*-inositol (11), essential fatty acids (12,13), vitamins, protein kinase C inhibitors, vasodi-

lators (14), antiprostaglandins (15), nerve growth factors (16), ACE inhibitors, lipid-lowering agents, advanced glycation end product inhibitors (17), acetyl-L-carnitine (18), and α -lipoic acid (ALA) (19)—the drug studied here.

Prevention or amelioration of positive neuropathic sensory symptoms deserve attention because symptoms are troublesome; create anxiety and depression; interfere with work, activities of daily living, meeting family and social responsibilities, and attaining adequate rest and sleep; and bring patients to see their medical provider (20).

Because there already are drugs that relieve positive neuropathic sensory symptoms (e.g., analgesics, antidepressants, tranquilizers, anti-epileptic agents, sedatives, or opiates), putative ancillary treatments should relieve symptoms by improving the pathophysiology of nerve and not by causing nerve injury. With prolonged use they might also be expected to prevent or improve neuropathy (20). Here we test whether positive neuropathic sensory symptoms can be ameliorated by the potent antioxidant ALA that has additional favorable metabolic actions (21–25). Racemic ALA, 6,8-dithioctane (the active ingredient studied here) is widely distributed in biological tissues and has a low toxicity profile (26–30). In dosages ranging from 100 to 1,800 mg/day (given orally or intravenously), ALA has been used extensively in medical practice in Germany since 1959, and it is considered to be safe and efficacious for the treatment of diabetic polyneuropathy symptoms (29–32). Using the improved approaches learned from the performance of earlier therapeutic trials we here retest whether intravenous ALA is efficacious for treatment of the positive neuropathic sensory symptoms of pain, paresthesia, and asleep numbness. Further, assuming that the drug is efficacious, we examined whether this effect is attributable to improved pathophysiology of nerve or to a different mechanism (i.e., degeneration of sensory nerve fibers).

Study design and demographic characteristics of patients

This is a mono-center, randomized, doubly masked, parallel-designed study of intravenous ALA versus placebo given in 14 doses over 3 weeks on the positive neuropathic sensory symptoms of burning and lancinating pain, asleep numbness, and

Table 1—Symptoms* and scoring† of the TSS (31)

Frequency	Intensity			
	Not present	Mild	Moderate	Severe
Occasionally	0	1.00	2.00	3.00
Often	0	1.33	2.33	3.33
Continuous	0	1.66	2.66	3.66

*The symptoms scored: sticking or lancinating pain, burning, prickling, or asleep numbness. Each of these is a positive neuropathic sensory symptom.
†Scoring: total score 0–14.64.

prickling (Total Symptoms Score [TSS]) of feet or legs in 120 patients (60 patients per group, 18–74 years old) with symptomatic (stage 2) diabetic polyneuropathy. Patients had to have type 1 or 2 diabetes (according to American Diabetes Association criteria); HbA_{1c} <12%; a TSS (Table 1) \geq 7.5 points (of a possible maximum of 14.64 points); neurologic signs (neuropathy impairment score [NIS] \geq 2 points, described below); nerve conduction or heart pulse deep breathing (HP-DB) abnormality; and during the run-in period (the first week), the TSS must not improve by \geq 3 points. Patients were excluded if they had confounding neurologic disease or neuropathy; symptomatic peripheral vascular disease; or clinically complicating cardiac, pulmonary, gastrointestinal, hematologic or endocrine disease, or malignancy.

Initially, one of us (R.S.) presented the outline of the study to Moscow endocrinologists. Of the names provided, 790 were interviewed by telephone, 497 were prescreened, 206 were screened, and 120 patients were admitted to the hospital study unit for the 4-week study. They signed informed consent to receive either the drug or placebo with double masking; however, for the first week, all patients received placebo. After randomization, on Monday of week 2 and thereafter for 14 treatments, as shown in Fig. 1, patients received either racemic ALA (600 mg) or placebo (0.04 mg of riboflavin, to give the solution a straw color to match ALA), each made-up to a final volume of 225 ml with physiologic saline and given intravenously over 30 min. The solutions were prepared by the sponsoring company (ASTA Medica, Inc., now Viatrix Inc.), shipped in a concentrated form to the study site identified only by coded num-

ber, and diluted to the final volume. In weeks 2 and 3, infusions were given daily, Monday through Friday; and in the fourth week, only four infusions were given (Monday through Thursday). Patients followed their usual diabetic surveillance and treatment regimens during the conduct of the study. Physicians were encouraged to reduce HbA_{1c} to levels below 8 or 9%, but patients were not excluded if this degree of control had not been achieved. Vital signs, weight, and metabolic alterations (especially diabetic, hepatic, and renal alterations) were monitored before, during, and after treatment.

Assessment of neuropathic end points

The primary end point was the TSS, which is a summation of the presence, severity, and duration of lancinating pain, burning pain, prickling, and asleep numbness (Table 1). TSS was evaluated daily (just before infusion and on treatment days) by the same neurologist (M.N.) in order to reduce interobserver variability. Standard questioning and scoring was used. Secondary end points, evaluated before and during the first week and at the end of the fourth week, were the NIS, the NIS of lower limbs [NIS(LL)], neuropathic symptoms of lower limbs (neuropathy symptoms and change of lower limbs [NSC(LL)], nerve conduction, and HP-DB; each of these end points was assessed twice, at onset and at end of the study.

The NIS is the sum score of a standard group of examinations of muscle weakness (0 = normal to 4 = paralyzed); reflex loss (0 = normal and 2 = absent with reinforcement); and touch-pressure, vibration, joint position and motion, and pinprick (0 = normal and 2 = absent and for each modality) of index finger and great toe and is scored for both sides of the body. Age, sex, physical fitness, and anthropomorphic features are to be taken into account in making judgements of abnormality. Typically, persons without neuropathy would have a score of 0. A person with mild weakness of toe extensors (1 and 1) and ankle dorsiflexor muscles (1 and 1), absent ankle reflexes (2 and 2), and decrease of all four sensory modalities of the great toes (4 and 4) would have a score of 16 points. The NSC scores (number, severity, and change) are derived from answers to 38 questions (muscle weakness, Q1–19; sensation, Q20–29; and autonomic symptoms, Q30–38)

Total Symptom Score, mean values and 1 SD

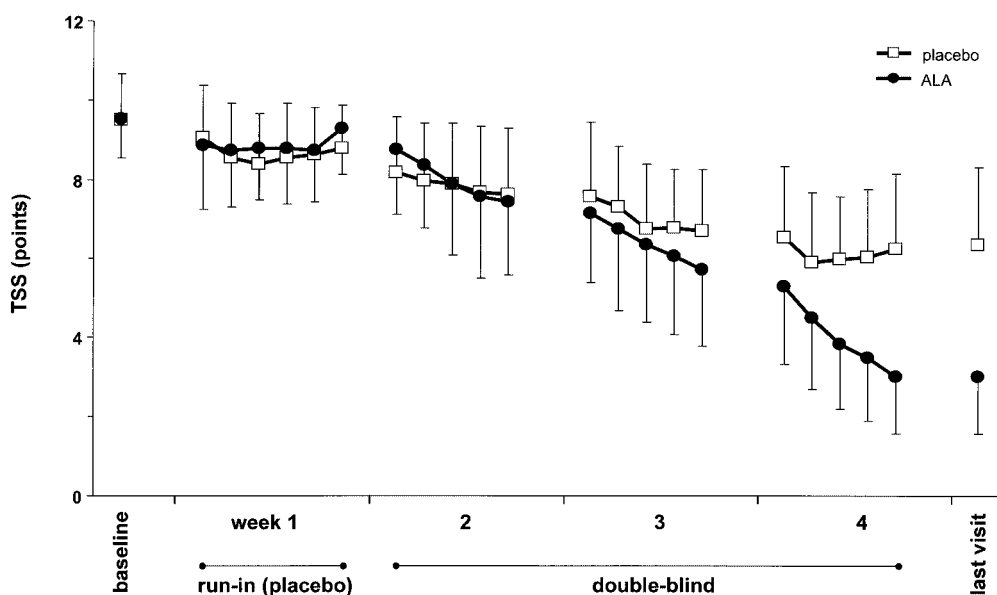


Figure 1—ALA (intravenous racemic ALA, 600 mg/day, 5 days/week) was given on the 14 treatment days as shown. Placebo (intravenous riboflavin in physiologic saline) was also given on the 14 treatment days. The color, rate of infusion, and total volume was essentially similar between placebo and ALA. Most patients reported that they thought they had received ALA, although only one-half had.

(20). The questions are also subdivided by anatomical site (head and neck, chest, upper limbs and lower limbs); by large fiber sensory function; by small fiber sensory function; by positive sensory symptoms (Q23–29 and separable by five sites); by negative sensory symptoms (Q20–22 for five sites); and by pain (Q25–29 for five sites). Number equals number of symptoms (of 38), and severity equals number × severity (1 = mild, 2 = moderate, and 3 = severe). Change in number and severity is obtained by subtracting the mean of the two end values from the mean of the onset values. The change score is the patient's comparison of the symptoms at last evaluation to the symptoms at onset (unchanged = 0, improved [1 = slightly, 2 = moderately, or 3 = much], or worsened [–1, –2, or –3]). The NSC (number, severity, and change) are independent measures of symptoms, whereas the remainder of the scores are subscores. Experienced and certified (by P.J.D. and colleagues) neurologists (A.B. and M.N.) evaluated the NIS and NSC.

The nerve conduction, QSTs, and autonomic tests were performed by trained and certified personnel (by W.J.L., P.J.D., P.A.L., and colleagues). All neurologic, nerve conduction, and QST results were interactively evaluated by the Reading and Quality Assurance Centers (at Mayo Clinic and Health Partners). Eligibility, baseline conditions, waveforms, stimulus

response patterns, and test values were also assessed.

Analysis plan

Based on previously reported results (33,34), the study was designed for 120 patients (60 in each group) to achieve 80% power to detect a difference between treatment groups of 1.0 point of the primary end point, assuming a SD of 1.8 points. The primary end point was change in TSS from the first day of treatment to the termination visit. The corresponding primary analysis for comparing the treatment groups was a two-sample *t* test at the 0.05 level. All results are reported as two-sided tests.

Regression analysis was also used, including treatment group, sex, and duration of diabetes as independent variables to account for imbalance (albeit small and

not significant for duration) between treatment groups with respect to the latter two variables. Wilcoxon's rank-sum tests were used to compare groups with respect to continuous secondary end points because many of these were highly skewed. χ^2 tests were used to compare treatment groups for dichotomous variables.

The analysis followed the intent-to-treat (ITT) principle. A per protocol analysis was also conducted for the primary end point.

RESULTS

Patient characteristics

These are shown in Table 2. No patients needed to be excluded after the first week because they were hyper-responders. During the trial, one patient was withdrawn from study because of fever (later

Table 2—Patient characteristics

	ALA	Placebo	P
n	60	60	NS
Age (years)	56.8 ± 9.65	55.4 ± 8.66	NS
Sex (M/F)	14/46	24/36	0.06
Type of diabetes (1/2)	15/45	15/45	NS
Duration of diabetes (years)	15.1 ± 8.8	14.0 ± 8.2	NS
Duration of neuropathy (years)	3.7 ± 6.0	3.4 ± 3.9	NS
Height (cm)	163.9 ± 8.01	167.3 ± 9.74	NS
BMI (kg/m ²)	29.4 ± 4.93	29.3 ± 5.23	NS

Data are means ± SD.

Table 3—Neuropathy symptom and change (NSC) scores

Score	Mean at onset (points)		Mean change (points)		Wilcoxon P value
	ALA*	PLA	ALA	PLA	
NSC—number	9.4	10.1	−4.2	−2.2	<0.001
NSC—severity	18.4	20.5	−11.1	−7.2	<0.001
NSC—change	0.2	0.0	14.5	9.2	<0.001
NSC Weakness—severity	0.0	0.0	0.0	0.0	NS
NSC Sensory—number	7.2	7.6	−3.3	−1.4	<0.001
NSC Sensory—severity	14.9	16.4	−9.4	−5.7	<0.001
NSC Sensory—change	0.2	0.0	12.4	7.4	<0.001
NSC(LL) Sensation—severity	14.9	5.5	−9.4	−5.7	<0.001
NSC(LL) Large-Fiber Sensation—severity	2.8	3.1	−1.2	−0.6	<0.001
NSC(LL) Small-Fiber Sensation—severity	12.1	13.3	−8.3	−5.1	<0.001
NSC(LL) Negative Sensation—severity	2.7	3.5	−1.2	−0.7	0.043
NSC(LL) Positive Sensation—severity	12.2	12.9	−8.3	−5.0	<0.001
NSC(LL) Pain—severity	10.0	10.6	−7.3	−4.6	<0.001
NSC Autonomic—severity	3.5	4.2	−1.7	−1.5	NS

*n = 60; PLA, placebo, n = 58.

attributed to an upper respiratory viral infection) and a second because of cardiac arrhythmia (later diagnosed as paroxysmal supraventricular tachycardia). Both had been on placebo. Following completion of the study, six patients were found to have laboratory values just outside the acceptable range (five had received placebo and one ALA). The results, therefore, were evaluated as ITT, including persons with protocol violations and as per protocol (PP), excluding the six patients). Because the results of ITT and PP were essentially alike, only the results of ITT are shown.

Adverse events

Of the 120 patients, 8 experienced a total of 11 adverse events: 4 with or immediately following treatment events, during the single-blind run-in phase; 1 with ALA; and 3 with placebo. No adverse event (AE) was judged to be causally related to the trial medication.

Efficacy

At baseline, there were no significant demographic, anthropomorphic, or disease differences between treatment groups except for a higher ratio of men to women in the placebo group (Table 2). After 14 treatments over 3 weeks, the mean value of the primary end point (TSS) had improved by a mean of 5.72 points (± 1.53) for ALA and a mean of 1.83 points (± 1.97) for placebo ($P < 0.001$) (Fig. 2).

The difference between treatment groups remained statistically significant ($P < 0.001$) in regression analysis taking into account the greater preponderance of females in the ALA group. A very small but statistically significant difference ($P = 0.021$) favoring ALA was first observed on the fourth treatment day, with the degree of the difference increasing and remaining significant thereafter (Fig. 1). Each of the four component symptoms of the TSS was assessed individually, and significantly greater improvement was found, favoring ALA over placebo, for each of them.

The NSC score, a 38-question survey of motor, sensory (positive and negative), and autonomic symptoms, was used as an independent measure of change of neuropathic symptoms (20). The mean change of motor or autonomic scores (number, severity, and change) was not significantly different between ALA and placebo. By contrast, large and statistically significant greater improvement of positive pain (stabbing, deep aching, burning, and excessive tenderness to contact or pressure; prickling; and asleep- numbness) and negative (loss of tactile, thermal, and pain sensation) neuropathic sensory symptoms had occurred with use of ALA as compared with placebo (Table 3). Also, patients' judgement of symptom change from baseline was significantly larger for ALA than for placebo ($P < 0.001$). ALA also improved the following

symptom scores to a better degree than did placebo at the $P < 0.001$ level: NSC(LL)—number, severity, and change; NSC(LL) Sensation—number and change; NSC(LL) Large-Fiber Sensation—change; NSC(LL) Small-Fiber Sensation—number and change; NSC(LL) Negative Sensation—number; NSC(LL) Positive Sensation—number and change; NSC(LL) Pain—number and change; NSC(LL) Small-Fiber + Autonomic—number, severity, and change. Significant at the 0.05 level: NSC(LL) Large-Fiber Sensation—number; NSC(LL) Negative Sensation—change.

Another secondary measure, the NIS, improved by 2.7 points (± 3.37) in ALA and by 1.2 points (± 4.14) in placebo ($P < 0.001$), but the NIS of lower limbs did not quite reach statistical significance ($P = 0.076$). Significant differences were not found between ALA and placebo for change in individual or composite scores of attributes of nerve conduction except for distal latency of the sural nerve, which improved more in the ALA (mean beginning minus end difference of -0.86 ms) than in placebo (mean difference of 0.353 ms, $P = 0.017$). No significant change was found for QST or for autonomic test results.

The treating physician graded the response to treatment in the ALA group as very good or good in 66.7% and as satisfactory in 33.3%; whereas for placebo, the judgements were very good or good in 1.7%, satisfactory in 68.3%, unsatisfactory in 26.7%, and not assessable in 3.3% ($P < 0.001$).

Patients judged overall efficacy following ALA as very good or good in 80% and as satisfactory in 20%. For placebo, the ratios and percents were very good or good in 8.3%, satisfactory in 73.3%, and unsatisfactory in 15%; two patients were not assessed. The difference in percent of very good or good versus other was significantly better ($P < 0.001$) for the ALA group.

The beneficial effect of ALA on neuropathic symptoms could not be attributed to a greater improvement in metabolic control. The HbA_{1c} of the ALA group had improved (from onset to end) by a mean value of 0.22%, whereas the placebo group had improved by a mean value of 0.12% ($P < 0.05$).

CONCLUSIONS— Various end points have been used to assess efficacy

in treatment trials of diabetic polyneuropathy: sum scores of neurologic abnormalities (e.g., the NIS), QSTs, nerve conduction, autonomic tests, combinations of these, and morphometry of nerve. In the present study, we use positive neuropathic sensory symptoms using TSS. An Ad Hoc Panel on End points for Diabetic Neuropathy Trials (20) had previously defined positive neuropathic sensory symptoms, discussed their use as trial end points, cited approaches for their assessment, and defined the degree of change that might be considered clinically meaningful and able to meet standards for being efficacious in controlled trials. Assuming that in such a trial the study was rigorously performed and doubly masked, it would be necessary to first show a statistically significant degree of symptom change for the trial drug above that found for the placebo; the degree of change should be of sufficient magnitude to be considered meaningful and should not have been due to worsening of neuropathy.

In using the TSS, a four-item measure of positive neuropathic sensory symptoms, as the primary outcome, as done here, we imply that these symptoms alone may be serious and debilitating health outcomes irrespective of the degree of neuropathic findings or impairments. It is increasingly recognized that positive neuropathy sensory symptoms are separate phenomena from negative symptoms (loss of tactile, thermal, pain, or other sensations) or from severity of neuropathic signs or impairments. Thus, for some patients with onset of polyneuropathy, positive symptoms may predominate without or with only a few neuropathic findings. Later, as positive neuropathic sensory symptoms abate, negative symptoms and impairments may become evident and worsen. Also, we note that these positive sensory symptoms may be more bothersome than negative neuropathic sensory symptoms, may inspire patients seeking relief from pain to visit physicians, and may be more debilitating (interfering with meeting work, family, and social responsibilities) than negative symptoms or impairments. These positive neuropathic symptoms are thought to be due to small-fiber sensory nerve fiber involvement. Although it is known that analgesics and anti-epileptic and tranquilizing medications may relieve positive neuropathic sensory symptoms, we here test the idea

that symptoms may be improved by another mechanism, e.g., by improving the pathophysiology of nerves.

The present study appears to show an unequivocal and large beneficial effect of intravenous racemic ALA on the frequency and severity of the positive neuropathic sensory symptoms due to diabetic polyneuropathy, the effect of which cannot be attributed to placebo or to worsening of polyneuropathy. The conclusion that the improvement is indicative of pharmacological efficacy comes also from the observations that the effect was statistically significant, was found for each component of the TSS, and was confirmed by similar results from independent assessments of symptoms using a separate clinical instrument (NSC) and that the improvement was sufficiently large to be considered meaningful by standards set by an ad hoc consensus panel (20). Additionally, efficacy was suggested by the time course of improvement (it was delayed and then increasingly improved over the treatment period, not rapidly, and then static or fading as would be expected with analgesics and opiates) (35), negative sensory symptoms and neuropathic impairment also improved, and the effect could not be explained by bias (patients had remained masked). Additionally, further analysis indicated that the treatment effect could not be explained by the unequal distribution by gender.

This beneficial effect from ALA had previously been reported (see references in ref. 22). By comparison with earlier studies, the present study was more rigorous in the following respects: a placebo run-in phase, pretraining and certification of investigators, interobserver variability was reduced by use of a single investigator performing critical end point evaluations, retention of essentially all patients throughout the study, use of reading and quality assurance of neuropathic end points, independent analysis of results, and evidence that masking was maintained.

Since it is generally thought that abnormalities of attributes (or composite scores) of nerve conduction or of HP-DB are among the most sensitive indicators of diabetic polyneuropathy, why did these end points not show statistically significant improvement with use of ALA? Why did QST not show improvement? To begin with, one attribute (sural nerve la-

tency) did show statistically significant improvement. Also, recognition of worsening by nerve conduction assessment may be more sensitive than recognition of improvement, and the latter may take more time. Thus, in the Diabetes Control and Complications Trial (DCCT), a statistically significant difference in nerve conduction was not recognized until several years had elapsed (6,7). In human neuropathies, it is common clinical experience that improvement or recovery of nerve conduction may lag well behind clinical improvement.

The mechanisms underlying the improvement of positive neuropathic sensory symptoms was not studied here, but antioxidant activity appears to be the likely mechanism. There is accumulating evidence from experimental animal and tissue culture studies that full radical-mediated oxidative stress is implicated in the pathogenesis of diabetic polyneuropathy by inducing neurovascular defects that result in endoneurial hypoxia and subsequent nerve dysfunction (36–39). Administration of physiological antioxidants, including ALA, a potent lipophilic free radical scavenger (40,41), provides a basis for a potential therapeutic effect. Diabetic peripheral nerves demonstrate footprints of oxidative stress and respond to treatment with lipoic acid (42). More recently, these findings have been supplanted by immunocytochemical evidence of DNA damage and cellular localization (43). Reduced oxygen species cause irreversible DNA damage to specific proteins. In recent years, antibodies have been generated against modified structures specific for reactive oxidative species-induced damage (43). The epitopes include 8-hydroxy-2'-deoxyguanosine and 4-hydroxy-2-nonenal-modified protein (44). Urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) has been reported to be increased in human diabetes (45,46).

Finally, the lack of toxicity to ALA in our trial is perhaps not surprising since several million dosages of the drug have already been given by German physicians, and toxicity appears to be extremely low (29,30). No toxicity was recognized in the present trial.

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