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Thioctic acid for patients with symptomatic diabetic polyneuropathy: a critical review.

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Abstract

Diabetic neuropathy represents a major health problem, as it is responsible for substantial morbidity, increased mortality, and impaired quality of life. Near-normoglycemia is now generally accepted as the primary approach to prevention of diabetic neuropathy, but is not achievable in a considerable number of patients. A growing body of evidence suggests that oxidative stress resulting from enhanced free-radical formation and/or defects in antioxidant defense is implicated in the pathogenesis of diabetic neuropathy. Markers of oxidative stress such as superoxide anion and peroxynitrite production are increased in diabetic patients in relation to the severity of polyneuropathy. In experimental diabetic neuropathy, oxygen free-radical activity in the sciatic nerve is increased, and treatment with thioctic acid, a potent lipophilic antioxidant, results in prevention or improvement of the diabetes-induced neurovascular and metabolic abnormalities in various organ systems. Pharmacodynamic studies have shown that thioctic acid favorably influences the vascular abnormalities of diabetic polyneuropathy such as impaired microcirculation, increased indices of oxidative stress, and increased levels of markers for vascular dysfunction, such as thrombomodulin, albuminuria, and nuclear factor-kappaB. Thus far, seven controlled randomized clinical trials of thioctic acid in patients with diabetic neuropathy have been completed (Alpha-Lipoic Acid in Diabetic Neuropathy [ALADIN I-III], Deutsche Kardiale Autonome Neuropathie [DEKAN], Oral Pilot [ORPIL], Symptomatic Diabetic Neuropathy [SYDNEY], Neurological Assessment of Thioctic Acid in Neuropathy [NATHAN] II) using different study designs, durations of treatment, doses, sample sizes, and patient populations. Recently, a comprehensive analysis was undertaken of trials with comparable designs that met specific eligibility criteria for a meta-analysis to obtain a more precise estimate of the efficacy and safety of thioctic acid (600mg intravenously for 3 weeks) in diabetic patients with symptomatic polyneuropathy. This meta-analysis included the largest sample of diabetic patients (n = 1258) ever to have been treated with a single drug or class of drugs to reduce neuropathic symptoms, and confirmed the favorable effects of thioctic acid based on the highest level of evidence (Class Ia: evidence from meta-analyses of randomized, controlled trials). The following conclusions can be drawn from these trials: (i) short-term treatment for 3 weeks using intravenous thioctic acid 600 mg/day reduces the chief symptoms of diabetic polyneuropathy to a clinically meaningful degree; (ii) this effect on neuropathic symptoms is accompanied by an improvement of neuropathic deficits, suggesting potential for the drug to favorably influence underlying neuropathy; (iii) oral treatment for 4-7 months tends to reduce neuropathic deficits and improve cardiac autonomic neuropathy; and (iv) clinical and postmarketing surveillance studies have revealed a highly favorable safety profile of the drug. Based on these findings, a pivotal long-term multicenter trial of oral treatment with thioctic acid (NATHAN I) is being conducted in North America and Europe to investigate effects on progression of diabetic polyneuropathy, using a clinically meaningful and reliable primary outcome measure that combines clinical and neurophysiological assessment.

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