

Alpha-Lipoic Acid Improved Polyneuropathy Symptoms

Symptoms improved as early as 1 week with the highest dose.

REVIEWED BY DAN ZIEGLER, MD, FRSCPE

Oral treatment with the antioxidant alpha-lipoic acid improved neuropathic symptoms and deficits in diabetic patients with distal symmetric polyneuropathy.

Dan Ziegler, MD, FRCPE, from the German Diabetes Clinic, German Diabetes Center, Leibniz Institute at the Heinrich Heine University in Dusseldorf, Germany, and colleagues, conducted a multicenter, randomized, double-blind, placebo controlled trial of 181 patients with diabetes in Russia and Israel. Patients were assigned once-daily oral doses of alpha-lipoic acid 600 mg, 1,200 mg, 1,800 mg or placebo for 5 weeks after a 1-week run in period, according to a report in *Diabetes Care*.

The primary outcome measure in the trial was the change from baseline in the Total Symptom Score (TSS), which included stabbing pain, burning pain, paresthesia and asleep numbness of the feet. "Secondary endpoints included individual symptoms of TSS, Neuropathy Symptoms and Change score (NSC), Neuropathy

Research suggests that alpha-lipoic acid may confer several health benefits. The antioxidant is found in plant and animal sources.

Impairment Score (NIS) and patients' global assessment of efficacy," the researchers wrote.

Mean TSS was similar among the treatment groups at baseline, on average, and decreased by 4.9 points in the 600-mg alpha-lipoic acid group (51%), 4.5 points in the 1200-mg group (48%) and 4.7 in the 1,800-mg group (52%) compared with 2.9 points (32%) among the placebo group ($P < .05$ vs all placebo).

"The corresponding response rates ($\geq 50\%$ reduction in TSS) were 62%, 50%, 56% and 26%, respectively," Professor Ziegler wrote. "Significant improvements favoring all three

ALPHA-LIPOIC ACID: A PRIMER

Alpha-lipoic acid is also known as thioctic acid. It is a disulfide compound that is a cofactor in vital energy-producing reactions in the body. It is a potent biological antioxidant and was once thought to be a vitamin for animals and humans. It is made endogenously in humans, however the details of its synthesis are not fully understood. In certain situations, for example diabetic polyneuropathy, alpha-lipoic acid might have condition-

al essentiality. Recent research indicates that the antioxidant roles of alpha-lipoic acid may confer several health benefits. It is found widely in plant and animal sources.

Most of the metabolic reactions in which alpha-lipoic acid participates occur in mitochondria. These include the oxidation of pyruvic acid (as pyruvate) by the pyruvate dehydrogenase enzyme complex and the oxidation of alpha-ketoglutarate by the alpha-ketoglutarate dehy-

alpha-lipoic acid groups were also noted for stabbing and burning pain, the NSC score, and the patients global assessment of efficacy. The NIS was numerically reduced.”

Whether the observed favorable short-term effect of alpha-lipoic acid on nerve pain and deficits can be translated into slowing the progression of diabetic neuropathy long term is unknown, the authors wrote. “However, our finding that neuropathic deficits such as impaired sensory function were improved is encouraging, because these are major risk factors in the development of neuropathic foot ulcers.”

The authors also said that, in the absence of a dose

response and because higher doses resulted in increased rates of gastrointestinal side effects, 600 mg once daily seems to be the most appropriate oral dose. ■

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drogenase enzyme complex. It is also a cofactor for the oxidation of branched-chain amino acids (leucine, isoleucine and valine) via the branched-chain alpha-keto acid dehydrogenase enzyme complex.

MECHANISM OF ACTION

Alpha-lipoic acid and its reduced metabolite, dihydro-lipoic acid (DHLA), form a redox couple and may scavenge a wide range of reactive oxygen species. Both alpha-lipoic acid and DHLA can scavenge hydroxyl radicals, the nitric oxide radical, peroxynitrite, hydrogen peroxide and hypochlorite. Alpha-lipoic acid, but not DHLA, may scavenge singlet oxygen, and DHLA, but not alpha-lipoic acid, may scavenge superoxide and peroxy reactive oxygen species.

Alpha-lipoic acid has been found to decrease urinary isoprostanes, O-LDL and plasma protein carbonyls, markers of oxidative stress. Further, alpha-lipoic acid and its redox couple DHLA have been found to have antioxidant activity in aqueous, as well as in lipophilic regions, and in extracellular and intracellular environments. Finally, with regard to alpha-lipoic acid's antioxidant activity, alpha-lipoic acid appears to participate in the recycling of other important biologic antioxidants, such as vitamins E and C, ubiquinone and glutathione.

Exogenous alpha-lipoic acid has been shown to increase ATP production and aortic blood flow during reoxygenation after hypoxia in a working heart model. It is thought that this is due to its role in the oxidation of pyruvate and alpha-ketoglutarate in the mitochondria, ultimately enhancing energy production. This activity, and possibly its antioxidant activity, may account for its possible benefit in diabetic polyneuropathy.

INDICATIONS AND USAGE

Lipoic acid shows evidence of being effective in the

treatment of diabetic neuropathy and may be useful in treating some other aspects of diabetes. It may help prevent the oxidation of LDL cholesterol and may be protective, generally, against oxidative stress and, specifically, against atherosclerosis, ischemia-reperfusion injury and various radiologic and chemical toxins. It may also be useful in some inborn metabolic disorders. There is less evidence that it might be helpful in some neurodegenerative conditions. There is preliminary evidence that it might have some immune-modulating effects. It has been suggested that lipoic acid may slow aging of the brain and that it may be an anti-aging substance, in general.

RESEARCH SUMMARY

Lipoic acid is an approved treatment for diabetic neuropathy in Germany. Numerous studies in both animals and humans have produced promising results with lipoic acid in this neuropathy. In animal models and culture studies, lipoic acid has demonstrated antioxidant properties that help reduce or eliminate a sequence of events that include reduced endoneural blood flow and oxygen tension, which are pre-requisites of neuropathy. In addition, some of these studies have revealed favorable lipoic acid effects that appear to be independent of its antioxidant properties, including increased glucose uptake, promotion of new neurite growth and chelation of transition metals thought to play a role in diabetic neuropathy.

Because of lack of long-term safety data, alpha-lipoic acid should be avoided by pregnant women and nursing mothers.

Those with diabetes and problems with glucose intolerance are cautioned that supplemental alpha-lipoic acid may lower blood glucose levels. Blood glucose should be monitored and antidiabetic drug dose adjusted, if necessary, to avoid possible hypoglycemia. ■

PDR Health. Available at: www.pdrhealth.com/drug_info/nmdrugprofiles/nutsupdrugs/alp_0159.shtml. Accessed on: Dec. 7, 2006.