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StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.

Alpha-Lipoic Acid

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Last Update: January 26, 2024.

Continuing Education Activity

Alpha-lipoic acid (ALA) is a supplement for managing chronic diseases characterized by oxidative stress, notably diabetic neuropathy, and demonstrates promise in slowing the onset of metabolic syndrome through antioxidant properties. This supplement exhibits multifaceted features, functioning as an antioxidant by mitigating oxidative stress-induced damage linked to chronic metabolic disorders. This activity elucidates the diverse indications, mechanism of action, contraindications, and crucial aspects of ALA supplementation, providing an understanding for healthcare team members to manage chronic oxidative stress-related conditions.

The in-depth exploration of ALA's mechanisms and therapeutic implications for oxidative stress-related chronic disorders, particularly diabetic neuropathy and metabolic syndrome, equips healthcare professionals with essential insights. Optimizing outcomes for chronic metabolic disorders associated with oxidative stress requires a multidisciplinary approach that considers the diverse benefits and limitations of ALA.

Objectives:

- Identify the clinical conditions associated with oxidative stress where alpha-lipoic acid supplementation is beneficial, such as diabetic neuropathy, metabolic syndrome, and other chronic diseases linked to increased oxidative damage.
- Screen patients with chronic diseases, particularly diabetes mellitus, to assess their eligibility for alpha-lipoic acid supplementation, considering factors such as concurrent medications, allergies, and comorbidities.
- Implement appropriate strategies for alpha-lipoic acid administration, including dosage regimens, administration protocols, and monitoring techniques to ensure patient compliance and safety.
- Communicate the rationale, risks, benefits, and adverse effects of alpha-lipoic acid therapy with patients, ensuring informed consent and adherence to treatment plans.

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Indications

Alpha-lipoic acid (ALA) is a caprylic acid-derived antioxidant. The compound is synthesized in the mitochondria and is a cofactor in the enzymatic nutrient breakdown.[1] ALA is also available in red meat, beets, carrots, potatoes, spinach, and broccoli. ALA consists of a dithiol functional group that eliminates reactive oxygen species (ROS) by reducing the oxidized forms of other

antioxidants.[2] The organosulfur compound was discovered in 1937 when scientists found a type of bacteria that uses potato juice for reproduction.[3]

ALA has recently gained a reputation as an antioxidant. In the reduced form, dihydrolipoate reacts and neutralizes ROS, such as superoxide radicals, singlet oxygen, and hydroxyl radicals. Thus, ALA is highly beneficial in several oxidative-stress-associated conditions such as ischemia-reperfusion or radiation injury.[4]

Secondly, numerous studies have strongly supported the role of ALA in treating diabetic neuropathy. ALA does so by enhancing nitric oxide-mediated endothelium-dependent vasodilation, improving microcirculation in patients with diabetic polyneuropathy.[5] Additionally, when taken with avocado or soybean unsaponifiable compounds, ALA is shown to significantly suppress prostaglandin E-2 production, a key cytokine in the pathogenesis of inflammation.[6]

ALA possesses an excellent iron-chelation property. The thiol groups in ALA are responsible for chelating irons. By increasing the glutathione levels inside the cells, ALA and dihydrolipoate excrete toxins, especially toxic metals, into the body. Lipoic acid preferentially binds to Zn, Pb, and Cu. On the other hand, dihydrolipoate forms complexes with Fe, Zn, Hg, Pb, and Cu.[7]

So far, ALA has the most substantial evidence of the therapeutic effect in diabetic neuropathy and oxidative stress conditions. There is still a need for more studies on the benefits of other conditions such as HIV/AIDS, liver disease, and weight loss. According to the FDA, ALA is safe and effective, and promising uses can be explored in future studies.

FDA-Approved Indications

ALA has no approved indication as a dietary supplement available over the counter.

Mechanism of Action

The dithiolane ring dictates ALA's chemical reactivity. Two forms of ALA are oxidized lipoic acid (LA) and reduced dihydrolipoic acid (DHLA). Both are capable of scavenging a variety of ROS. DHLA is a potent antioxidant that can neutralize free radicals. Furthermore, ALA simultaneously regenerates other antioxidant factors, such as vitamins C and E, increasing glutathione synthesis.[7] ALA is generally involved in keto acid oxidative decarboxylation processes and is a growth factor for some organisms.[8]

In the pathogenesis of inflammation, factor NF-kB modulates inflammatory cytokines, including interleukins (ILs) such as IL-1β and IL-6. ALA inhibits I Kappa B kinase, suppressing the activation of inflammatory cytokines.[9]

Pharmacokinetics: Absorption, volume of distribution, metabolism, and excretion are not well-established for ALA.

Administration

ALA is available as an oral supplement and intravenous injection. Studies postulate promising therapeutic properties in several conditions, including type 1 and 2 diabetes mellitus (DM), neuropathy, and ischemic-perfusion injury.

Oral: Data demonstrates that daily oral supplementation of 300 mg of ALA over 3 months maintains and improves functional vision in type 1 and type 2 diabetes mellitus patients.

[10] However, ALA can be orally dosed between 600 mg and 1800 mg daily for up to 6 months.

Intravenous injection: The study shows evidence for IV treatment of 600 mg daily in improving positive neuropathic symptoms and neuropathic deficits.[11]

Special Patient Populations

Hepatic impairment: No research has examined the effects of hepatic impairment on ALA dosing. Research has examined ALA's role in treating certain liver conditions.[12][13]

Renal impairment: There is no research documenting dose adjustments of ALA for patients with renal impairment. Some research has examined the role of ALA and other compounds in reducing oxidative stress in diabetic nephropathy.[14]

Pregnant women: To date, research shows ALA supplementation during pregnancy is safe.[15] More data is needed to establish the role of ALA supplementation in pregnancy.

Breastfeeding women: There is a lack of reliable data regarding the safety of alpha-lipoic use during breastfeeding.

Pediatric and older patients: There is no data regarding the use of ALA in these specific patient populations.

Adverse Effects

ALA is considered a safe supplementation without any adverse effects. One study supports the safety of the drug, and an adult can take up to 2400 mg without experiencing any harmful adverse effects.[16] High doses of ALA are not recommended as higher doses provide no additional benefits. The most common adverse effects reported with ALA are headache, heartburn, nausea, and vomiting.[17]

A 1996 ALA study on 6 rhesus monkeys showed that excess lethal doses in primates would cause hepatic necrosis. Researchers noted that 3 out of 6 monkeys that received 90 mg/kg to 100 mg/kg of intravenous ALA exhibited large necrotic areas in the muscles of their thighs, the liver, the heart, and the kidneys. This situation led the researchers to conclude that exceptionally high doses of IV ALA can produce the same symptoms that smaller doses prevent.[18]

Contraindications

Box Warning

There are no box warnings for ALA.

Warnings and Precautions

There are very few studies on the contraindications of ALA supplementation. However, due to the adverse effects of ALA on animals and due to ALA's physiological effects, one should consult with a doctor if they have the following conditions:

- Liver disease
- Consumption of large amounts of alcohol
- Diabetes (ALA is known to lower blood sugar)
- Thyroid disorder

- Thiamine deficiency

Also, one should stop using ALA immediately if an allergic reaction occurs, such as skin rash, nausea, or vomiting. There is no established contraindication for using ALA in pregnant women and infants.

Monitoring

Though ALA intoxication is extremely rare, close monitoring is necessary for children who are around diabetic patients. A case of ALA intoxication was reported in which the patient attempted to commit suicide. Therefore, it is vital to monitor ALA use in people who have suicidal thoughts or psychological issues.[19] Patients admitted to the emergency room with acute ALA poisoning usually present with tachycardia, neurologic effects, metabolic acidosis, and T wave inversion in the EKG.[20]

There is no established therapeutic index of ALA in humans. However, studies show that safety dosage is defined in animals. The experimental values are 400 mg/kg to 500 mg/kg for dogs, 30 mg/kg for cats, and 500 mg/kg for mice. In animal studies, high levels of ALA were reported to cause hepatotoxicity, apathy, confusion, and hypokinesis.[7] Therefore, patient monitoring may be advisable when under high doses of ALA.

Toxicity

ALA is generally considered a safe drug. A daily dose of 200 mg/day to 2400 mg/day of ALA is deemed safe without significant adverse effects. However, there is no reported safe dose in children.[21]

A notable case in literature demonstrated status epilepticus (SE) that subsided within a few days. The seizures were treated per normal standards for SE.[22]

In the last 2 decades, there have been few reported cases of ALA toxicity in humans. Most of these cases occur in children and are treatable. Though there is no established lethal dosage of ALA for humans, studies have shown that a high dose of 121 mg/kg body weight/day was associated with alterations in liver enzymes and liver function.[16] Therefore, there are potentially harmful adverse effects from overdosing on ALA, and more studies are necessary to determine the toxicity.

Enhancing Healthcare Team Outcomes

Effective and safe use of ALA supplements require communication between healthcare team members, including primary care clinicians and pharmacists. Patients should consult their primary clinician before using ALA, and these frontline resources can provide patients with the proper dosage and safety information. ALA is a generally safe supplement that can be purchased over the counter, but clinicians can monitor and treat any adverse events. It is essential to have appropriate cooperation between interprofessional team members to ensure that the patient receives optimal benefits from ALA supplementation.

Review Questions

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Disclosure: Hiep Nguyen declares no relevant financial relationships with ineligible companies.

Disclosure: Mark Pellegrini declares no relevant financial relationships with ineligible companies.

Disclosure: Vikas Gupta declares no relevant financial relationships with ineligible companies.

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