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Alpha Lipoic Acid: A potential therapeutic option for painful peripheral neuropathies

By Dr. Jessica Curcio

Abstract

• Peripheral neuropathy (PN) is a major public health concern.
• There are many etiologies for PN including injury, infection, toxicity, genetics, metabolic disease and nutritional deficiencies.
• Alpha lipoic acid (ALA), also known as thioctic acid, is a potent antioxidant and cofactor in many cellular metabolic processes.
• Oxidative damage plays a significant role in the pathogenesis of both diabetic peripheral neuropathy (DPN) and chemotherapy induced peripheral neuropathy (CIPN).
• Because of the antioxidant capability, ALA has been studied for its potential benefit in preventing and treating PN.

Literature Review

• Neuritic pain is “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system either at peripheral or central level” (Baumann et al., 2011).
• Symptoms of numbness, tingling and pain often first in the distal lower extremities and progressing proximally (Rossetti & Abdelbaki, 2013).
• Pathogenesis of Diabetic Peripheral Neuropathy (PN) include oxidative stress and mitochondrial dysfunction, and reactive oxygen species and result in damaging effect on mitochondria as well as DNA (Carrasco, Cortes, Chonard, & Cavalletti, 2014).

Peripherial Neuropathy

• Neuritic pain is an important clinical challenge in both diabetics and patients undergoing chemotherapy.
• The symptoms include burning, tingling, shooting pains as well as numbness.
• These symptoms are often debilitating and cause a significant impact on quality of life, morbidity and mortality in these populations.
• Studies have reported that up to 50% of diabetic patients and up to 80% of patients receiving chemotherapy will experience PN (Argyros, Brenna, Mantero, & Cavalletti, 2010; Torsey & Shervagur, 2012).
• Thromboprophylactic use of ALA has been studied for its efficacy in preventing and treating PN.
• Alpha lipoic acid has many antioxidant and cofactor in many cellular metabolic processes.

• In patients with peripheral neuropathy can alpha lipoic acid to another therapy improve neuropathy symptoms?

Statement of the Problem

• Oxidative stress is thought to play a critical role in the development of CIPN. Amelioration of this response and accommodation to reactive oxygen species is a significant delay oxidant stress (Cavalletti, 2014).

Alpha Lipoic Acid and Diabetic Peripheral Neuropathy

• 1180 patients and when examined as a group the data from pooled studies suggest that 600 mg of intravenous ALA daily for 3 weeks improved sensory symptoms and neuropathic deficits (Müller & Rüther, 2011; Mittermair, Kollen, Alkadah, Kleffner, & Bilò, 2012).
• A prospective observational study compared carbamazepine, gabapentin, or ALA and followed over 6 months. Gabapentin and ALA outperformed carbamazepine, however the pregabalin group had a faster onset of symptom improvement. Lower dose, 200mg, ALA was used (Pati, Mishra, Patil, & Dikshit, 2014).
• A retrospective study examined the effects of switching patients on ALA 600 mg for 5 years to gabapentin. In the treatment group 45% of the patients had to decrease their dose for neuropathic pain vs. the placebo group (Pati et al., 2014).
• This particular study was not able to reach completion due to the dropout of patients from both treatment and placebo groups.

Research Question

• Two smaller studies found benefit in combination treatment of ALA with other antioxidants (Botbolito & Massowe, 2012; Vaudanov et al., 2014).
• A prospective study examined ALA alone pregabalin and carbamazepine (Pati et al., 2014). This group used a lower dose of ALA, only 200 mg orally per day, than had been previously reported efficacy which is 600 mg per day (Mijchoud et al., 2012). ALA did prove efficacious at symptom improvement, however pregabalin surpassing ALA in speed of onset.
• Two large RCT that were published by the same group. The first, found that the lower dose of 600 mg was not by improved symptom scores while minimizing GI effects (Ziegler et al., 2008b). The second failed to demonstrate any meaningful response of ALA vs placebo after 4 years. However, this was in part due to lack of progression of PN symptoms in the placebo group (Ziegler et al., 2011). This study did demonstrate improvement overall in the treatment group from baseline.
• The inclusion and analysis of earlier studies of ALA and DPN demonstrates a clear benefit using 600mg ALA daily with improvement starting as early as 3 weeks and with limited side effects (Ziegler et al., 2004). Studies published more recently do support the previous findings, however given the inconsistent study designs and poor power, larger studies should be performed before broad recommendations.
• A recent meta-analysis has examined the effects of ALA on CIPN are encouraging. Rodent models of CIPN and ALA have demonstrated efficacy in reversing allopurinol and hypothyroidism (Joseph et al., 2008; Torsey et al., 2013). Another animal study supports these finding demonstrating that ALA increases pain threshold and improves strength in CIPN (Bhathal et al., 2013). One recent study was even able to demonstrate that pre-treatment with ALA prevented allopurinol (Torsey et al., 2013).
• The human clinical trial data for ALA and CIPN is very limited. Results of two small pilot studies did demonstrate that 600 mg of ALA for 3 weeks followed by 600 mg ALA three times daily for 6 weeks resulted in reduced symptoms of CIPN in more than half of the patients (Gudlicka et al., 2002; Gudlicka, Komr, Schmid, & Scheither, 2008). In contrast, more recently a study failed to demonstrate that ALA could attenuate the development of CIPN (Gao et al., 2013b). This particular study was not able to reach completion due to the dropout of patients from both treatment and placebo groups.

• Despite how common PN is and the burden of the disease, currently there is no efficacious way to halt the progression of the disease, other than tight glucose control in diabetes.
• ALA is a potent antioxidant and has been used for decades in Germany as an approved treatment for DPN. Studies have demonstrated the efficacy of ALA for symptoms of DPN and it has an excellent safety profile.
• It would seem reasonable that one could offer patients the option of using ALA for DPN for a three month trial, if not cost prohibitive, particularly if side effects from conventional medications are too cumbersome.
• No solid evidence to support the use of ALA for CIPN. There is some concern with using antioxidants during chemotherapeutic and radiation treatment regimens.
• However, CIPN is a significant complication from chemotherapy and can be quite devastating to patients. Current treatments offered, including SSRI’s, TCA’s and sodium channel blockers have not proven to be greatly effective.
• Given that, further studies must be designed that examine the potential for ALA in treating CIPN. Until then, we must be guarded against broad recommendations for ALA in CIPN.

Applicability to Clinical Practice

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References


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