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Alpha Lipoic Acid: A Potential Therapeutic Option for Painful Peripheral Neuropathies

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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

Introduction

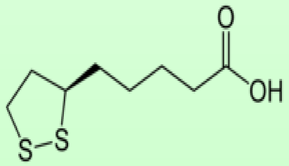
- Peripheral neuropathy is prevalent among diabetic patients and patients receiving chemotherapy.
- PN is a conduction deficit that affects the peripheral nerves secondary to damage of the nerve axons or myelin sheaths.
- The affected nerves can be either sensory or motor.
- Affected sensory neurons can be either the small sensory receptors, which affect pain and temperature sensation or large sensory fibers, which lead to a deficit in proprioception and vibration.

Statement of the Problem

- Peripheral neuropathy 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 (Argyriou, Bruna, Marmiroli, & Cavaletti, 2012; Tesfaye & Selvarajah, 2012).
- Therapeutic options thus far include antidepressants, anti-epileptic and opioid analgesics, that have limited efficacy for PN but cause a variety of unwanted side effects.

Research Question

- In patients with peripheral neuropathy can alpha lipoic acid vs no/other therapy improve neuropathic symptoms?



Literature Review

Peripheral Neuropathy

- Neuropathic pain is "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system either at peripheral or central level" (Haanpaa et al., 2011).
- Symptoms of numbness, tingling and pain often first in the distal lower extremities and progressing proximally (Hosseini & Abdollahi, 2013).

Pathogenesis of Diabetic Peripheral Neuropathy

- DPN is common affecting up to 50% of diabetics the economic burden exceeds ten billion dollars per year (Rathur & Boulton, 2005).
- In DPN chronic hyperglycemia creates oxidative stress in overlapping pathways. This includes; the polyol, hexosamine and protein kinase C pathways (Edwards, Vincent, Cheng, & Feldman, 2008).
- The generation of free radicals resulting in oxidative stress is thought to be a major contributor to the development of DPN (Yagihashi, Mizukami, & Sugimoto, 2011).

Pathogenesis of Chemotherapy Induced Peripheral Neuropathy

- Chemotherapeutic agents also lead to peripheral neuropathy as a fairly common side effect. This is a serious complication that can lead to reduction in dose or discontinuation of life-saving therapy (Rock & DeMichele, 2003).
- Oxidative stress is thought to play a critical role in the development of CIPN. Chemotherapeutic drugs result in the enhancement and accumulation of reactive oxygen species and result in damaging effect on mitochondria as well as DNA (Carozzi, Canta, Chiorazzi, & Cavaletti, 2014).

Mechanism of Action of Alpha Lipoic Acid

- An antioxidant is defined as "any substance that, when present in very low concentrations compared to that of an oxidizable substrate, significantly delays or inhibits the oxidation of that substrate" (Halliwell & Gutteridge, 1995).
- ALA acts as a potent antioxidant with the ability to scavenge ROS (Gomes & Negrato, 2014).

Alpha Lipoic Acid and Diabetic Peripheral Neuropathy

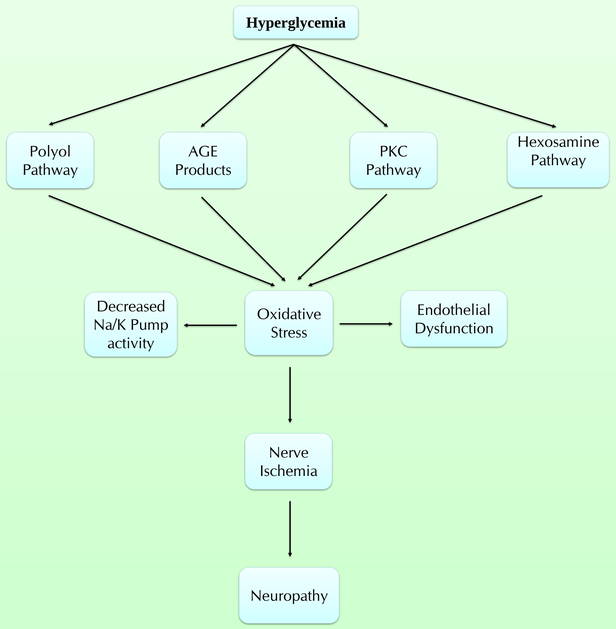
- 1160 patients and when examined as a group the data from pooled studies suggest that 600 mg of intravenous ALA daily for 3 weeks improved sensory symptoms and neuropathic deficits.(McIlduff & Rutkove, 2011; Mijnhout, Kollen, Alkhalaf, Kleefstra, & Bilo, 2012).
- A prospective observational study compared carbamazepine, pregabalin, or ALA and followed over 6 months. Pregabalin and ALA outperformed carbamazepine, however the pregabalin group had a faster onset of symptom improvement. Lowers dose, 200mg, ALA was used (Patel, Mishra, Patel, & 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 discontinue the gabapentin due to SE. Gabapentin was associated with more frequent visits, higher cost and greater side effect without any added efficacy benefit (Ruessmann & German Society of out patient diabetes centres AND (Arbeitsgemeinschaft niedergelassener diabetologisch tatiger Arzte e.V.), 2009).
- Multicenter RCT determined that oral ALA was effective in the treatment of DPN in a non-dose dependent manner. Further the study found that 600 mg/day would be the optimum dose of ALA to use as it was efficacious and lacked significant GI side effects (Ziegler et al., 2006a).
- Multicenter RCT, to determine the impact of ALA on diabetic peripheral neuropathy over 4 years. The study failed to demonstrate any difference between treatment groups. (Ziegler et al., 2011).

Alpha Lipoic Acid and Chemotherapy Induced Peripheral Neuropathy

- Pilot study investigated the therapeutic potential of ALA for cumulative CIPN in patients being treated with oxaliplatin. Patients received 600 mg of intravenous ALA weekly for 3-5 weeks and then 600 mg three times a day orally. The study found the 53% of the patients reported that the side effect of CIPN was effectively reduced. (Gedlicka, Scheithauer, Schull, & Kornek, 2002).
- Pilot study examined the potential for ALA to counteract docetaxel plus cisplatin found that almost 43% of the patients had improvement in symptoms with a median response time of 4 weeks (Gedlicka, Kornek, Schmid, & Scheithauer, 2003a).
- RCT examined if ALA could attenuate the risk of developing severe PN symptoms in patients treated with platinum-based chemotherapy. Patients were randomly assigned to 600 mg of ALA orally vs placebo while receiving chemotherapy and followed over 24 weeks. The study failed to demonstrate any significant difference between treatment and placebo in preventing neurotoxicity. At the end of the study only 28% of the treatment group and 30% of the placebo group remained for statistical analysis. (Guo et al., 2013a).

Discussion

- Two smaller studies found benefit in combination treatment of ALA with other antioxidants (Bertolotto & Massone, 2012; Vasudevan et al., 2014).
- A prospective study examined ALA against pregabalin and carbamazepine (Patel et al., 2014). This group used a lower dose of ALA, only 200 mg orally per day, than had been previously reported as efficacious which is 600 mg per day. (Mijnhout et al., 2012). ALA did prove efficacious at symptom improvement, however pregabalin outperformed ALA in speed of onset.
- Two larger RCT that were published by the same group. The first, found that the lower dose of 600mg orally per day improved symptom scores while minimizing GI effects (Ziegler et al., 2006b). 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.
- Animal studies that have examined the effects of ALA on CIPN are encouraging. Rodent models of CIPN and ALA have demonstrated efficacy in reversing allodynia and hyperalgesia (Joseph et al., 2008; Trevisan et al., 2013). Another animal study supports these finding demonstrating that ALA increases pain threshold and improves strength in CIPN (Bhadri et al., 2013). One rodent study was even able to demonstrate that pre-treatment with ALA prevented allodynia (Trevisan 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 iv ALA for 3 weeks followed by 600 mg ALA three times daily orally effectively reduced symptoms of CIPN in more than half of the patients (Gedlicka et al., 2002; Gedlicka, Kornek, Schmid, & Scheithauer, 2003b). In contrast, more recently a study failed to demonstrate that ALA could attenuate the development of CIPN (Guo et al., 2013b). This particularly study was not able to reach completion due to the dropout of patients from both treatment and placebo groups.



Applicability to Clinical Practice

- Despite how common PN is and the burden of the disease, currently there is no efficacious way to halt the progression of the development, 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 also 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.

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