

Alpha lipoic acid: a new treatment for neuropathic pain in patients with diabetes?

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ABSTRACT

Background: Neuropathic pain is difficult to treat. We identified those studies in the literature in which the effectiveness of alpha lipoic acid as a treatment for neuropathic pain was evaluated.

Methods: Systematic literature review. The databases MEDLINE and EMBASE were searched using the keywords “lipoic acid”, “thioctic acid”, “diabet*”, and the medical subject headings (MeSH) “thioctic acid” and “diabetes mellitus”. Randomised placebo-controlled trials (RCTs) and meta-analyses were selected and assessed for their methodological quality.

Results: Five RCTs and one meta-analysis were found. The Total Symptom Score (TSS) was used as the primary outcome measure. A significant improvement in the TSS was reported in four of the RCTs. An oral or intravenous alpha lipoic dose of at least 600 mg per day resulted in a 50% reduction in the TSS. However, compared with the control group, the TSS reduction in most groups was less than 30%, which is the threshold presumed to be clinically relevant. Four RCTs were of good quality (level of evidence 1b), one RCT had methodological limitations (level 2b), and the methodological quality of the meta-analysis was insufficient for the purposes of this review.

Conclusion: Based on the currently available evidence, when given intravenously at a dosage of 600 mg once daily over a period of three weeks, alpha lipoic acid leads to a significant and clinically relevant reduction in neuropathic pain (grade of recommendation A). It is unclear if the significant improvements seen after three to five weeks of oral administration at a dosage of ≥ 600 mg daily are clinically relevant.

KEYWORDS

Alpha lipoic acid, diabetes mellitus, neuropathic pain

INTRODUCTION

Neuropathy is a microvascular complication of diabetes mellitus which leads to considerable morbidity and a decreased quality of life. Peripheral neuropathy starts with the toes and spreads to the feet and the lower legs.¹ Besides decreased sensation, which is a risk factor for the development of neuropathic foot ulcers, neuropathic pain can also be a sign of polyneuropathy. Neuropathic pain can present as tingling, burning, pain, and cramps. There is overwhelming evidence that the likelihood of developing microvascular complications is related to the level of glucose dysregulation over an extended period of time.² Hyperglycaemia induces an increased production of free oxygen radicals in the mitochondria (oxidative stress), which leads to the activation of the four known pathways to hyperglycaemic damage: the polyol, hexosamine, protein kinase C, and AGE pathways.³ These lead to damage of endothelial and neuronal cells. Antioxidants, such as alpha lipoic acid, could theoretically be effective in treating diabetic neuropathy.

Neuropathic pain is difficult to treat, and does not usually respond to standard analgesics.⁴ The medications currently used to treat neuropathic pain in patients with diabetes mainly include antidepressants, antiepileptics, and opioids. These medications are limited in their effectiveness, have considerable side effects, and they have no effect on the processes by which hyperglycaemia leads to cell damage.⁵ In 1951, alpha lipoic acid was identified as a coenzyme in the tricarboxylic acid cycle (Krebs cycle).⁶ Alpha lipoic acid

is also a potent antioxidant, reported to reduce diabetic microvascular and macrovascular complications in animal models.^{7,8} A recent study in humans with type 1 diabetes mellitus showed a normalisation of the increased AGE formation and a reduction of the hexosamine pathway.⁹ By preventing the damage caused by hyperglycaemia, alpha lipoic acid may not only be an analgesic treatment but may also improve nerve function. Besides, compared with the medications currently in use, alpha lipoic acid has few side effects.¹⁰

MATERIALS AND METHODS

On 11 May 2009, three of the authors (GSM, AA, and NK) conducted a search for relevant publications in the electronic database MEDLINE, using the search engine *PubMed*, and EMBASE. The search strategy used in MEDLINE used the terms “lipoic acid”, “thioctic acid”, “diabet*”, and the MeSH terms “thioctic acid” and “diabetes mellitus” (*table 1A*). A similar search strategy was used in EMBASE (*table 1B*). The search results were combined in PubMed with a sensitive filter for randomised controlled trials (RCTs) and systematic reviews. In EMBASE, the filter “evidence based medicine” was applied which searched for Cochrane Reviews, Controlled Clinical Trials, Meta Analyses, Randomised Controlled Trials, and Systematic Reviews. The Cochrane Library was also searched for systematic reviews. All the authors obtained the same results. For study selection, the following inclusion criteria were used: 1) randomised controlled trials or systematic reviews on alpha lipoic acid, 2) a study population consisting of patients with diabetes mellitus and peripheral neuropathic pain, and 3) use of the total symptom score (TSS) as the primary outcome measure. The following exclusion criteria were used: 1) animal studies and 2) articles not written in English. GSM, AA, and NK independently selected

which studies were to be included in the review by checking the titles and abstracts downloaded from the databases. A consensus meeting was then held to resolve any disagreements. The final decision to include or exclude any study was based on the article’s full text. The reference lists of the identified studies were reviewed to discover additional potentially eligible studies. Unpublished data and conference proceedings were excluded from this review. The aforementioned authors proceeded to independently evaluate the quality of each study using the standardised evaluation form for RCTs and systematic reviews developed by the Dutch Cochrane Centre (www.cochrane.nl) (*table 4*). The levels of evidence and recommendation grades were applied according to the Oxford Centre of Evidence-based Medicine, version 2001 (<http://www.cebm.net/index.aspx?o=1025>).

RESULTS

Identification and selection of studies

The search yielded 215 publications in PubMed and 98 in EMBASE. After reviewing the titles and the abstracts, ten randomised placebo-controlled trials on alpha lipoic acid in patients with diabetic neuropathic pain were selected. These studies were identified in both MEDLINE and EMBASE. After reading the complete articles, two studies were excluded,^{11,12} because they dealt with the effects of alpha lipoic acid on autonomic instead of diabetic neuropathy. Two additional studies were excluded because the articles were not written in English.^{13,14} One study¹⁵ was excluded because the TSS was not used as the outcome measure. One systematic review¹⁶ was found in both MEDLINE and EMBASE and included. No systematic reviews were found in the Cochrane Library. A protocol for a proposed systematic review was found in the Cochrane Library.¹⁷ There was no disagreement among the reviewers regarding the studies selected for inclusion.

Randomised controlled trials

The study populations in the five selected RCTs were all made up of patients with peripheral diabetic neuropathy.¹⁸⁻²² The age range was from 18 to 74 years, and most of the patients included had type 2 diabetes mellitus. The effects of orally administered alpha lipoic acid were investigated in three studies, intravenous administration in two studies, and a combination of oral and IV administration was investigated in one study (*table 2*). The dosage of alpha lipoic acid ranged from 100 to 1800 mg per day. Intravenous alpha lipoic acid was given for three weeks, and oral administration varied between three weeks and six months. The primary outcome measure was the total symptom score (TSS). The TSS is a questionnaire in which the patient is asked to assess the intensity (absent, mild, moderate, severe)

Table 1A. Search strategy used in PubMed to identify randomised controlled trials investigating the effect of alpha lipoic acid on diabetic neuropathy

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((lipoic acid OR thioctic acid OR thioctic acid[MeSH]) AND
(diabete* OR diabeti* OR diabeto* OR diabetes mellitus[MeSH]))
AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR
clinical trials[MeSH Terms] OR clinical trial[Publication Type]
OR random*[Title/Abstract] OR random allocation[MeSH Terms]
OR therapeutic use[MeSH Subheading])
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Table 1B. Search strategy used in Embase

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((lipoic acid OR thioctic acid) AND (diabetes mellitus OR
diabetic*)) AND ((cochrane review)/lim OR [controlled clinical
trial]/lim OR [meta analysis]/lim OR [randomized controlled
trial]/lim OR [systematic review]/lim))
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Table 2. Overview of randomised, placebo-controlled studies with alpha lipoic acid in persons with symptomatic peripheral diabetic neuropathy

Study 1 st author, year; study name	Research group		Length of study	Alpha lipoic acid dosage	Admini- stration route	Primary outcome measure	Findings		Difference interven- tion vs control* (signifi- cance)	Level of evidence
	Patient type	Number of patients (inter- vention/ control)					Intervention	Control		
Ziegler 1995 ALADIN	DM2; 18-70 yr	328 (65/63/ 66/66)	3 weeks	a) 100 mg daily b) 600 mg daily c) 1200 mg daily	IV	TSS	a) 7.6→4.3 b) 7.8→2.8 c) 7.6→3.1	6.8→4.2	-0.7 (ns) -2.4 (p<0.001) -1.9 (p=0.003)	1b
Ruhnau 1999 ORPIL	DM2; 18-70 yr	24 (12/12)	3 weeks	600 mg tid	Oral	TSS	7.99→4.24	8.18→6.24	-1.81 (p=0.021)	1b
Ziegler 1999 ALADIN III	DM2; 18-65 yr	509 (167/174 / 168)	3 weeks + 6 months	a) 600 mg iv daily for 3 wks, then 600 mg tid orally for 6 months b) 600 mg iv daily for 3 wks then placebo tid orally for 6 months	IV & oral	TSS	After 3 weeks: a+b) 8.2→4.5 After 7 months: a) 8.1→4.1 b) 8.3→4.3	After 3 weeks: 8.4→5.4 After 7 months: 8.4→4.4	-0.7 (ns) 0 (ns) 0 (ns)	2b
Ametov 2003 SYDNEY	DM1+ DM2; 18-74 yr	120 (60/60)	3 weeks	600 mg daily for 14 days	IV	TSS	-5.72	-1.83	-3.89 (p<0.001)	1b
Ziegler 2006 SYDNEY 2	DM1+ DM2; 18-74 yr	181 (45/47/ 46/43)	5 weeks	a) 600 mg daily b) 1200 mg daily c) 1800 mg daily	Oral	TSS	a) 9.44→4.59 b) 9.40→4.90 c) 9.02→4.32	9.27 → 6.35	-1.93 (p<0.05) -1.58 (p<0.05) -1.78 (p<0.05)	1b

*Calculated differences between intervention and control groups - not controlled. DM = diabetes mellitus ; ns = non significant; IV=intravenous; TSS = total symptom score; tid = 3 times a day.

and the frequency (now and then, often, continuous) of four symptoms (pain, burning, paresthesia, numbness) resulting in a scaled score in which 0 means no symptoms and 14.64 means that all four symptoms are severe and more or less continuously present. A 30% change on this scale is considered to be clinically relevant (or ≥ 2 points in patients with a starting score ≤ 4 points).¹⁸ A significant improvement in the TSS scores was reported in four of the five studies. In these studies an average 50% reduction was seen in the TSS with the oral or intravenous administration of a minimum of 600 mg per day. However, when compared with the subjects in the control groups, the reduction in TSS was actually less than the clinically relevant threshold of 30%,¹⁸ as the TSS in the control group also decreased. This was particularly evident in the studies where the alpha lipoic acid was administered orally. In one study, in which the alpha lipoic acid was administered intravenously, the intervention group did show a more than 30% reduction in TSS when compared with the control group.¹⁹ Dosages higher than 600 mg per day did not result in a further improvement in the TSS, and resulted in a greater incidence of side effects

such as nausea, vomiting, and dizziness. The side effects seen with dosages ≤ 600 mg per day were no different than was seen with placebo.

Methodological quality of the randomised controlled trials

A survey of the methodological quality assessment is shown in *table 4*. Four of the RCTs¹⁸⁻²¹ were of good methodological quality (level 1b). One RCT²² had methodological limitations (level 2b), with too many patients dropping out of the study, carrying with it the risk of selective loss to follow-up with influence on the results through exclusion bias. When we leave this study out of our assessment, we are left with four level 1b RCTs: two investigating oral^{20,21} and two investigating intravenous^{18,19} administration of alpha lipoic acid.

Systematic reviews / meta-analyses

We found one meta-analysis of four RCTs in which it was concluded that three weeks of treatment with intravenous alpha lipoic acid (600 mg/day) led to a significant decrease in reported neuropathic pain.¹⁶ No

Table 3. Total Symptom Score (TSS): scoring system for neuropathic symptoms (pain, burning, paresthesiae and numbness)

Symptom frequency	Symptom intensity			
	Absent	Slight	Moderate	Severe
Occasional	0	1.00	2.00	3.00
Frequent	0	1.33	2.33	3.33
(Almost) continuous	0	1.66	2.66	3.66

The score can range from 0 (no symptoms) to maximally 14.64 (all symptoms present, severe, continuous).

Table 4. Methodological quality assessment of the intervention studies

	Ziegler 1995 ALADIN	Ruhnau 1999 ORPIL	Reljanovic 1999 ALADIN II	Ziegler 1999 ALADIN III	Ametov 2003 SYDNEY	Ziegler 2006 SYDNEY 2
1	Randomisation?	Yes	Yes	Yes	Yes	Yes
2	Concealment of allocation?	Yes	Yes	Yes	Yes	Yes
3	Patients blinded?	Yes	Yes	Yes	Yes	Yes
4	Doctors blinded?	Yes	Yes	Yes	Yes	Yes
5	Investigators blinded?	No	No	Yes	No	No
6	Groups comparable at baseline?	Yes	Yes	Yes	Yes	Yes
	If not, correction for this in analysis?					
7	Follow-up complete of >80% of patients?	Yes	Yes	No	No	Yes
8	Intention-to-treat analysis?	No*	Yes	Yes	No	Yes
	Level of evidence	1b	1b	2b	2b	1b

* per protocol analysis, but did not differ from intention-to-treat analysis.

studies investigating the effect of oral administration were included. The meta-analysis did not fulfil the requirements of the Cochrane Collaboration. No search strategies were reported, the search was not conducted using MEDLINE, the publications were not selected by two reviewers independently, and the quality of the studies to be included was not evaluated. The results for clinically heterogeneous studies were combined without the creation of any subgroups for the different dosages of alpha lipoic acid used in each study. We concluded that the methodological quality of this meta-analysis did not satisfy our requirements, and we did not include the results in our review.

DISCUSSION

Based on the four level 1b randomised, placebo-controlled studies included here, there is evidence to support that alpha lipoic acid causes a significant and clinically relevant decrease in neuropathic pain when administered for a period of three weeks at a dosage of 600 mg/day (grade of recommendation A). We can not conclude

that the significant improvements seen after the oral administration of alpha lipoic acid over a period of three to five weeks at a dosage of >600 mg per day are clinically relevant. More research will be required before definitive conclusions about the oral administration of alpha lipoic acid can be drawn. There are, at present, no publications in which the effects of long-term treatment with intravenous or oral lipoic acid are presented.

The RCTs and the meta-analysis addressing this subject matter come primarily from a single German group of researchers. A number of these studies were multicentre studies which included German as well as Russian, Israeli, and Croatian patients. There is not likely to be any overlap between these patient populations. All of the studies were sponsored by a pharmaceutical company which manufactures alpha lipoic acid. A number of the authors received salaries from this company, besides which, the pharmaceutical company also had representatives sitting on the advisory body for several of these studies. In Germany, alpha lipoic acid is registered as an accepted medication for the treatment of diabetic neuropathic pain and is covered by health insurance companies.

It is striking that clinically relevant effects on neuropathic pain are seen after only three to five weeks of alpha lipoic acid administration. This is unexpectedly rapid for an antioxidising diet supplement. The explanation for this is not clear from the evidence.

To investigate the long-term effects of alpha lipoic acid, long-term studies will be required. The continued, long-term effectiveness of any treatment is of the utmost importance for chronic conditions such as diabetic neuropathy. The possibility of a mechanism of action by which alpha lipoic acid may act to prevent neuropathic pain in high-risk patients is also worth further investigation.

Alpha lipoic acid is not covered by health insurance companies in the Netherlands, although it may be prescribed and ordered by pharmacies. The maximum dosage per capsule or tablet is 300 mg in the Netherlands. The cost of using alpha lipoic acid at a dosage of 600 mg/day varies between 17.15 and 75.00 euros per month, depending on the manufacturer. In comparison, the costs of amitriptyline, carbamazepine, duloxetine, gabapentine, and pregabalin are 3.41, 9.38, 35.80, 53.75, and 71.71, respectively, per month (based on the Z-index tax, August 2009).²³ Nothing has been published concerning qualitative manufacturer-dependent differences in alpha lipoic acid preparations. With the demonstrated efficacy of alpha lipoic acid, those patients with diabetic neuropathic pain who would benefit should be identified. Suitable compensation structures would then still need to be developed and applied for.

CONCLUSION

The intravenous administration of alpha lipoic acid leads to clinically relevant improvement of painful diabetic neuropathy in the short term. Unfortunately, there are not yet any results on its administration over a longer time period. The results we have seen are encouraging enough to recommend intravenous alpha lipoic acid for the treatment of diabetic neuropathy. The improvements seen with the oral administration of alpha lipoic acid are much less clearly described, and additional research will be necessary to investigate its effects. We do not recommend the use of orally administered alpha lipoic acid for the treatment of diabetic neuropathy at this time.

REFERENCES

1. Ziegler D. Treatment of diabetic neuropathy and neuropathic pain: how far have we come? *Diabetes Care*. 2008;31(Suppl):S255-61.
2. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577-89.
3. Brownlee M. The pathobiology of diabetic complications. A unifying mechanism. *Diabetes*. 2005;54:1615-25.
4. Bansal V, Kalita J, Misra UK. Diabetic neuropathy. *Postgrad Med J*. 2006;82:95-100.
5. Rutkove SB. A 52-year old woman with disabling peripheral neuropathy: review of diabetic polyneuropathy. *JAMA*. 2009;302:1451-8.
6. Reed LJ, DeBusk BG, Gunsalus IC, et al. Crystalline alpha-lipoic acid; a catalytic agent associated with pyruvate dehydrogenase. *Science*. 1951;114:93-4.
7. Lin J, Bierhaus A, Burgert P, et al. Effect of R-(+)-alpha-lipoic acid on experimental diabetic retinopathy. *Diabetologia*. 2006;49:1089-96.
8. Yi X, Maeda N. Alpha-lipoic acid prevents the increase in atherosclerosis induced by diabetes in apolipoprotein E-deficient mice fed high-fat/low-cholesterol diet. *Diabetes*. 2006;55:2238-44.
9. Du X, Edelstein D, Brownlee M. Oral benfotiamine plus α -lipoic acid normalises complication-causing pathways in type 1 diabetes. *Diabetologia*. 2008;51:1930-2.
10. Singh U, Jialal I. Alpha-lipoic acid supplementation and diabetes. *Nutr Rev*. 2008;66:646-57.
11. Ziegler D, Schatz H, Conrad F, et al. Effects of treatment with the antioxidant α -lipoic acid on cardiac autonomic neuropathy in NIDDM patients. *Diabetes Care*. 1997;20:369-73.
12. Tankova T, Koev D, Dakovska L. Alpha-lipoic acid in the treatment of autonomic diabetic neuropathy (controlled, randomized, open-label study). *Rom J Intern Med*. 2004;42:457-64.
13. Liu F, Zhang Y, Yang M, et al. Curative effect of α -lipoic acid on peripheral neuropathy in type 2 diabetes: A clinical study. *Nat Med J China*. 2007;87:2706-9.
14. Strokov IA, Kozlova NA, Mozolevskii IV, et al. The efficacy of the intravenous administration of the trometamol salt of thioctic (alpha-lipoic) acid in diabetic neuropathy. *Vserossiiskoe Obshchestvo Psikhiatrov*. 1999;99:18-22.
15. Reljanovic M, Reichel G, Rett K, et al. Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (α -lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II). *Free Rad Res*. 1999;31:171-9.
16. Ziegler D, Nowak H, Kempler P, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant α -lipoic acid: a meta-analysis. *Diab Med*. 2004;21:114-21.
17. Mirza N, Cornblath DR, Hasan S, et al. Alpha-lipoic acid for diabetic peripheral neuropathy (Protocol). *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD005492. DOI: 10.1002/14651858.CD005492.
18. Ziegler D, Hanefeld M, Ruhnau KJ, et al. Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant α -lipoic acid. *Diabetologia*. 1995;38:1425-33.
19. Ametov AS, Barinov A, Dyck PJ, et al. The sensory symptoms of diabetic polyneuropathy are improved with α -lipoic acid. *Diabetes Care*. 2003;26:770-6.
20. Ziegler D, Ametov A, Barinov A, et al. Oral treatment with α -lipoic acid improves symptomatic diabetic polyneuropathy. *Diabetes Care*. 2006;29:2365-70.
21. Ruhnau KJ, Meissnert HP, Finn JR, et al. Effects of 3-week oral treatment with the antioxidant thioctic acid (α -lipoic acid) in symptomatic diabetic polyneuropathy. *Diab Med*. 1999;16:1040-3.
22. Ziegler D, Hanefeld M, Ruhnau KJ, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant α -lipoic acid. *Diabetes Care*. 1999;22:1296-1301.
23. *Farmacotherapeutisch Kompas* 2009: <http://www.fk.cvz.nl/>.