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Original article

Increasing the bioavailability of (R)-α-lipoic acid to boost antioxidant activity in the treatment of neuropathic pain

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Summary. α-lipoic acid (α-LA) is a potent natural antioxidant because it has a broad spectrum of action towards a great many free radical species and boosts the endogenous antioxidant systems. Although it is a multi-functional molecule, its pharmacokinetic characteristics pose restrictions to its use in the treatment of oxidative stress-dependent pathologies. Formulations that increase the bioavailability of α-LA have a better potential efficacy as adjuvants for the treatment of these conditions. This objective was achieved with a liquid formulation for oral use containing only R-αLA, the natural enantiomeric and most active form of α-lipoic acid. For the first time, the effects of this formulation were evaluated on neuropathic pain, a symptom caused by an increase in oxidative stress, regardless of the underlying cause. Neuropathic patients who have used this dietary supplement noticed an improvement in their quality of life and a significant reduction was observed in a number of certain descriptive pain parameters (intensity, burning, unpleasantness, superficial pain). Undoubtedly further, more in-depth, studies need to be conducted; however, this first investigation confirms the role of R-αLA as an anti-oxidant for the treatment of peripheral neuropathy. Increasing its plasma bioavailability even after a non-invasive administration through the oral route is a good starting point for proposing a valid adjuvant for the treatment of pain symptoms. (www.actabiomedica.it)

Key words: (R)-α-lipoic acid; antioxidant; liquid formulation; bioavailability; neuropathic pain; neuropathic pain scale

Introduction

A number of factors influence the bioavailability of a drug administered via the oral route. This type of administration involves a number of different phases that restrict the amount of drug absorbed and made available to the various action sites: the disintegration of the solid formulation, the solubility and stability of the active substance in the gastric and intestinal environment, the inter-individual variability in absorption and, lastly, the metabolism of the first hepatic phase. The fraction of the drug that reaches systemic circulation can potentially be distributed in the various segments of the organism, where it will perform its biological function.

These factors represent a key point for the oral administration of antioxidant substances developed to prevent and/or counteract a number of pathologi-

cal or physiological conditions related to overt oxidative stress. The various species of free radical trigger a cascade mechanism that amplifies the cytotoxic effects leading to an alteration of cell structure and function. Therefore, the best antioxidant therapy is that which is based not merely on substances with a broad spectrum of action, but that also guarantees rapid absorption and bioavailability in order to more effectively counteract the effects induced by oxidative stress.

In this context, the study of molecules with an antioxidant activity goes hand-in-hand with the development of new formulations for oral use developed to increase the bioavailability of these substances and maintain therapeutic safety whilst making them more effective for the treatment of various diseases.

α-lipoic acid: a natural antioxidant

α-lipoic acid (ALA, 1,2-dithiolane-3-pentanoic acid, thioctic acid) (1-5) is a multi-functional molecule that is commonly used in clinical practice; in addition to being a known enzyme cofactor (6), it partecipates in the glucidic (3, 7) and lipid (8) metabolism and regulates the transcription of certain genes (9).

Due to oxidoreductive interconversion, it is present in a reduced form (ALA, α-lipoic acid) and an oxidative form (DHLA, α-dihydrolipoic acid), for which a scavenger activity has been observed for various different oxidising species. The ALA/DHLA system therefore boasts a broad spectrum of action (10). The antioxidant function of ALA is also performed by means of other cell mechanisms as *i)* it boosts the endogenous antioxidant systems, regenerating them and favouring their synthesis or cell availability (2,4, 11), *ii)* it chelates the heavy metals that can help cause oxidative stress (2, 4, 12) and *iii)* it participates in the biogenesis of the mitochondria, the organelles involved in energy metabolism and, consequently, the first targets of the free radical species generated during oxidative phosphorylation (13).

As a ubiquitous and versatile molecule, ALA acts, moreover, in all types of cell and in both hydrophobic and hydrophilic environments (1-5).

Despite being a potent antioxidant, as shown by *in vitro* and cell culture studies, ALA possesses certain characteristics that restrict its use in therapeutic protocols, thereby favouring its approval as a dietary supplement in certain countries, whilst being used as a medicinal product in others (1, 5, 14).

These limits can be attributed to the intrinsic properties of the molecule itself such as the instability of the raw material due to the opening of the dithiolane ring and subsequent formation of intermolecular disulfide bonds. The predominant formulative strategy adopted to avoid this polymerisation is to prepare racemic mixtures (R,S-ALA). Given the presence of an asymmetric carbon, it is possible to synthetically produce enantiomeric forms *R* (R-ALA) and *S* (S-ALA) that present different properties in processes, such as absorption, tissue distribution, degradation and elimination, that depend on chemical stereoselectivity (1, 2, 15).

Lastly, other characteristics that restrict the use of ALA after oral administration can be attributed to its low solubility in the gastric environment and high metabolism of the first hepatic phase responsible for its reduced plasma bioavailability.

A liquid (R)-α-lipoic acid formation for oral use

The main aim for the use of ALA in therapeutic protocols is therefore to improve bioavailability not only in quantitative terms by increasing the fraction of α-lipoic acid in the blood stream but also in qualitative terms by favouring the availability of the R enantiomer, the natural and most biologically active form of ALA.

In this sense, a good result was obtained with a liquid formulation for oral use, Liponax sol, containing only R-ALA prepared in a solution that improves its solubility and guarantees stability in the gastric environment (16, 17). As shown by the various pharmacokinetic profiles obtained using an animal model (17), it is clear that this formulation allows a high bioavailability of R-ALA, which remains in the plasma longer than a similar solid formulation (Figure 1).

Increasing the bioavailability and plasma persistence of α-lipoic acid after oral administration, in order to obtain a result as similar as possible to intravenous administration, would make it possible to im-

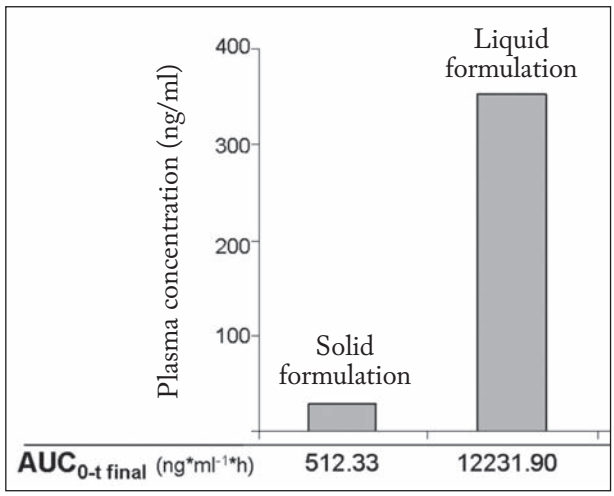

Figure 1. Plasma concentration 4 hours after oral administration and bioavailability (AUC $_{0\text{-}t(final)}$), in male Sprague-Dawley rats, of a 50 mg/kg dose solid or liquid formulation R-ALA. Modified from (17)

prove the efficacy observed to date for this antioxidant, especially in cases of oxidative stress-dependent conditions that, like peripheral neuropathy, require chronic treatment. The first indications obtained from studies on animal models confirmed that R-ALA in this liquid oral formulation obtains a more effective and rapid response on the recovery of sensory and motor nerve conduction velocity altered by diabetic neuropathy (17) or caused by chemotherapy such as oxaliplatin.

The therapeutic potential of α- lipoic acid: focus on peripheral neuropathies

ALA is increasingly proposed as a adjuvant in the treatment of many diseases by virtue of its pleiotropic properties that allow it to act on different fronts (1-5). The conditions that respond to treatment with α-lipoic acid are characterised by the presence of acclaimed oxidative stress or an altered biochemical and molecular mechanism (gene transcription, regulation of enzymatic or receptor activity), that can be regulated by α-lipoic acid. Ultimately, diseases with different aetiologies (for example, metabolic syndrome, obesity, diabetes, multiple sclerosis, heavy metal poisoning, etc.) (2, 18-21) or physiological conditions such as ageing (22) could benefit from common treatment with ALA.

For this reason, over the past few decades a number of studies have been conducted to transfer into clinical practice the indications identified using animal models, to evaluate the safety of ALA in humans and document its biological efficacy.

A more complete picture of the therapeutic effects of ALA can be obtained in the treatment of peripheral diabetic neuropathy, whose pathogenesis can be attributed to the oxidative stress triggered by hyperglycaemia (23-24).

In short, the lipids peroxidation and accumulation on the membrane receptors of terminally-glycated substances, the reduction in Na^+/K^+ ATPase pump activity, the change in homeostasis and calcium signalling, the increase in the polyol pathway that favours a deficit of endogenous antioxidants, the alteration of the endoneural blood flow and hypoxia are just some of the oxidative stress-dependent phenomena observed in the peripheral neuronal cells in animal models of diabetes. These factors determine an alteration in neuronal structure and consequently in biological functions such as neuronal conduction velocity or the perception of pain, which triggers neuropathic complications.

From the pioneering ALADIN study (25) through to the recent publication of meta-analyses (26- 27) it has been shown that intravenous administration of α-lipoic acid in diabetic patients causes a significant improvement, compared to placebo, in certain symptoms, such as burning, paraesthesia, numbness and pain, which are typical of peripheral neuropathy. On the other hand, the effects observed after oral administration are somewhat discordant between the various studies (26); greater efficacy is observed by prolonging the treatment time by several months/years or by increasing the dose of ALA, although the latter is associated with a higher undesirable effect rate (27). These considerations confirmed the therapeutic potential of ALA in humans, highlighting that the lower efficacy observed with oral administration can be primarily attributed to its pharmacokinetic characteristics.

Sensory symptoms (pain, numbness, tingling, burning, bound limb feeling, etc.) constitute a typical aspect of all forms of peripheral neuropathy as they represent the expression of an alteration in the physiology of the sensory fibres. They may persist, even on

an occasional basis, for a very long period, thereby affecting the patient's quality of life. Neuropathic pain is therefore a complication not merely of diabetic peripheral neuropathy, but also that caused by mechanical conditions (e.g., lumbocrural and/or cervicobrachial pain, carpal and tarsal tunnel) and that caused by chemotherapy (e.g., cisplatin and taxol) or of a viral origin (e.g. *Herpes zoster).* Although they have different aetiologies, these neuropathies are all characterised by damage caused by chronic oxidative stress (28-30) and therefore given the benefits observed in clinical studies on diabetic neuropathy, α-lipoic acid has been used with success also as an adjuvant for the treatment of compression neuropathies.

Improvements in the life's quality and reductions in pain symptoms have been reported by patients with cervicobrachial pain or lumbocrural sciatica even after oral therapy with a racemic form of α-lipoic acid and greater advantages with a solid formulation of the natural enantiomer R-ALA (31-33).

Liquid formulation of (R)-α-lipoic: an alternative treatment for neuropathic pain

The liquid oral formulation of R-ALA has the potential to coadjuvate the treatment of the pain symptoms that are typical of peripheral neuropathies.

One study, despite not being comparative and having been performed on a limited number of patients, confirms the tolerability and safety of this formulation in humans and represents an initial indication of its efficacy in the treatment of neuropathic pain. The group of 38 patients (22 women and 16 men) treated for 4 weeks with R-ALA oral liquid formulation (Liponax sol) was intentionally heterogeneous in terms of the clinical presentation of neuropathic pain. The patients were enrolled by practitioners specialising in various medical areas (diabetology, physical medicine, orthopaedics and rheumatology), who therefore had different experiences as regards diagnosis and, to a greater extent, in the therapeutic treatment of the condition. To this it can be added that today's doctors have to choose between a variety of painkillers, despite the lack of solid evidence of efficacy, and to evaluate the effects of the treatment proposed according to subject patient-reported rather than absolute parameters, such as the perception of the type of pain and evaluation of its intensity.

More particularly, 16 (42.1%) patients with diabetic neuropathy and 22 (57.9%) patients (of whom 13 were evaluated by the physiatrist specialist, 4 by the orthopaedist and 5 by the rheumatologist) with compression or entrapment-induced peripheral neuropathy were recruited. The diabetic patients were treated with hypoglicemic agents (e.g. insulin, metformin sulfanylurea, etc.) and some presented hypertension in addition to their metabolic symptoms (hypercholesterolaemia, hypertriglyceridaemia). None of the patients had been treated with other antioxidants in the months prior to the start of the study.

The mean age of the subjects enrolled was 60.76 (± 12.63) years, an age at which the endogenous antioxidant defence systems start to become inadequate to counteract radicals, which are undoubtedly increased due to the greater exposure to oxidant agents over time (22). Moreover, the endogenous synthesis of α-lipoic acid, and therefore the only natural form R-ALA, also drops with age (1), and in the elderly there is also a greater inter-individual variability in the gastrointestinal absorption of exogenous ALA (34).

The entity of the pain was quantified considering the ratings for neuropathic pain assessment recorded at the start of the study and after 4 weeks of oral treatment with a daily administration of 300 mg R-ALA liquid formulation.

We used a simplified form of the McGill Pain Questionnaire (MPG), a multidimensional scale whose descriptive parameters identify various aspects of the pain felt (35). Some of the items considered in this investigation are influenced to a greater degree by treatment with the oral liquid formulation, indicating a reduction in pain symptoms regardless of the cause of the diagnosed neuropathy. Certain parameters attributed to the qualitative description of symptoms, their intensity and the surface area involved are more sensitive to antioxidant therapy, to the extent that at the end of the study, pain was more localised and appears less unbearable, less sharp and less irritating.

An Italian version of the neuropathic pain scale (NPS), which was also validated to identify its possible clinical applications on a heterogeneous population

(36-37), was proposed as an additional instrument for verifying the effects of antioxidant analgesic therapy.

After 4 weeks of treatment with 300 mg of R-ALA in oral liquid formulation a statistically significant ($p<0.001$) reduction was observed in the total value obtained using the NPS (Tab. 1). More specifically, a significant reduction ($p<0.001$) was observed in a number of descriptive items of this scale and, in particular, for the parameters concerning intensity, burning, unpleasantness and superficial pain (Tab. 1).

In addition, during this investigation, it was observed that antioxidant therapy with liquid formulation R-ALA is most efficacious as an adjuvant for the treatment of pain symptoms in the group of patients with compression or entrapment-induced peripheral neuropathy and therefore recruited by the physiatrist, rheumatologist or orthopaedic specialist. This observation, which undoubtedly requires further investigation, should also be analysed in the light of the clinical condition of the more complex diabetic patients characterised by multiple complications that affect, and often underestimate, the perception of pain.

The pain symptom is not a separate factor rather, especially in the elderly, it is responsible for a number of consequences that contribute to worsening life's quality. Social constraints, difficulties walking, frequent painkiller use, loss of appetite, depression, anxiety and insomnia are the most common consequences observed in the population with painful neuropathy. We used a reduced version of the Therapy Impact Questionnaire (TIQ) (38) to record the effect of treatment with liquid formulation R-ALA on some of these parameters. At the end of the study there was a significant reduction in the descriptive parameters concerning the quality of sleep ("sleeping problems") and the individual's functional and emotive state (for example "feeling tired"), thereby helping to improve certain aspects of daily life. No adverse events or discontinuation of treatment were recorded; despite the intrinsic characteristics of α-lipoic acid, which has an unpleasant smell and is unpalatable, this liquid formulation is well tolerated and safe even in patients on politherapy such as diabetic subjects.

Discussion and conclusions

Neuropathic pain is characterised by chronic persistent symptoms, often accompanied by an abnormal sensitivity to pain stimuli (hyperalgesia) and exacerbations in the presence of sensations that are usually not painful (allodynia). This condition significantly com-

Table 1: Variation in neuropathic pain scale parameters after 4 weeks' treatment with 300mg/ day of oral formulation R-ALA. The values are indicated as mean ± standard deviation; the statistical significance (p value) was calculated using the Wilcoxon signed ranks test

Description of the pain	Neuropathic pain scale		p-value Wilcoxon Signed Ranks Test
	Value at start of the study	Value at end of the study	
Intense	5.71 (± 2.14)	4.05 (± 1.97)	<0.001
Sharp	4.13 (± 3.05)	3.47 (± 2.47)	0.053
Burning	4.79 (± 2.76)	3.42 (± 2.15)	<0.001
Dull	3.95 (± 2.76)	3.63 (± 2.75)	0.174
Cold	3.24 (± 2.72)	2.37 (± 2.35)	0.004
"Raw skin"	3.89 (± 3.22)	3.03 (± 2.85)	0.002
Itching	2.68 (± 2.84)	2.39 (± 2.30)	0.090
Unpleasant	5.66 (± 2.22)	4.13 (± 1.97)	<0.001
Deep	5.55 (± 2.67)	4.68 (± 1.97)	0.011
Superficial	5.29 (± 2.31)	4.11 (± 2.08)	<0.001
Total	44.89 (±12.76)	35.29 (±15.43)	<0.001

promises quality of life as it interferes with daily activities and sleeping. It has a significant impact on direct social costs related to the cost of treatment and indirect social costs due to the reduction in the ability to work.

The treatment that counteracts these symptoms and, at the same time, maintains and/or restores correct nerve fibre function compromised by oxidative stress and related complications will undoubtedly be most effective.

Regardless of the cause, the first to be affected by neuropathic damage are the sensory fibres, whose function alterations translate into phenomena such as tingling, burning, numbness, loss of sensitivity, etc. These phenomena represent a wake-up call for peripheral neuropathy and suggest the need to act as quickly as possible in order to increase the probability of success in recovering neuronal function and/or reducing damage. Motor fibre involvement, on the other hand, is a later phenomenon in neuropathy and is consequently an indicator of a more severe and more difficult to treat condition.

Over the past few decades, evidence has been accumulated encouraging the use of the natural and most active form of α-lipoic acid, R-ALA, as adjuvant for not only symptomatic but also in aetiological therapy for the treatment of peripheral neuropathy. By countering membrane lipid peroxidation and participating in energy metabolism, R-ALA exerts a neuroprotective and neurotrophic function that is essential for restoring the physiological biochemical processes altered by oxidative damage and, consequently, for overcoming certain symptoms typical of peripheral neuropathy.

In view of a therapeutic strategy for diabetic and/or compression-induced neuropathy, ALA has a further additional value in that it also acts on other aspects of the disease, to the extent that it is considered excessively simple to interpret its role in terms of its antioxidant function alone (1-5). I*n vitro* studies, also confirmed by animal models, have shown that R-ALA favours the glucose uptake to muscle cells and adipocytes (1-3, 7) and, albeit not significantly, affects the hyperglycaemia responsible for the mechanisms that trigger the neuropathic complications of diabetes (15, 17, 23-24). The severe hypoglycaemia recorded in literature following ALA supplementation, nevertheless falls within a cases related to Hirata syndrome or IAS (insulin autoimmune syndrome). This condition only occurs in genetically predisposed individuals, with a higher frequency in the Japanese population, and after prolonged use of any medicinal product/nutraceutical that, like ALA, contains sulfhydryl groups (39).

By means of a number of mechanisms that are still not entirely clear (e.g., regulation of cytokines), α-lipoic acid also exerts control on the inflammatory component that often accompanies peripheral neuropathies of mechanical origin (2, 40); in addition, by acting on the endothelial cells for example by producing nitric oxide, it improves the endoneural blood flow and favours the transport of nutrients to the compression site responsible for neuronal damage (2).

Despite presenting limits from various aspects, the study described in this article constitutes the first investigation designed to assess the effects of (R)-α-lipoic acid oral liquid formulation on peripheral neuropathies of various aetiologies, ranging from diabetic to mechanic origins (e.g., lumbocrural sciatica, carpal or tarsal tunnel). The results obtained confirm R-ALA's ability to provide relief from the pain symptoms of peripheral neuropathy, as is also anticipated by other data in literature (20, 21, 25-27, 29-31), and are encouraging for subsequent, larger studies aimed at confirming in humans what has already been observed in animal models of diabetic neuropathy. In this case, the high bioavailability and prolonged plasma persistence of R-ALA recorded after oral administration of the liquid formulation favour, compared to the solid formulations, a more effective recovery of the conduction velocity of sensory fibres and, albeit to a lesser extent, motor fibres (17). The formulative development has therefore made it possible to boost certain characteristics of R-ALA, thereby improving its pharmacokinetic parameters also by means of a non-invasive route of administration, such as the oral route (17).

Undoubtedly further studies must be conducted in order to record, on the basis of reproducible electrophysiological parameters, the recovery of neuronal damage; however, this first investigation shows that focusing on molecules, such as R-ALA that are able to exert a broad antioxidant action and neuroprotective function represents a good strategy for dealing with the pain symptoms of peripheral neuropathy and improving patients' quality of life.

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