Intravenous alpha-lipoic acid improves fructosamine level in type 2 diabetes patients

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INTRAVENOUS ALPHA-LIPOIC ACID IMPROVES FRUCTOSAMINE LEVEL IN TYPE 2 DIABETES PATIENTS

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Abstract

Aim. Alpha-lipoic acid (ALA) is a potent naturally occurring antioxidant and in the past years several studies suggested the fact that ALA can have positive effects on glucose metabolism. We intended to evaluate in an open-label, non-randomized study, in usual ambulatory settings, the effect intravenous ALA infusion on fructosamine level, in patients with type 2 diabetes and painful peripheral diabetic neuropathy.

Patients and methods. 28 consecutive patients with type 2 diabetes and painful peripheral diabetic neuropathy, treated with 10 daily infusions of 600 mg ALA in 300 ml of normal saline, were included in the study. Fructosamine was measured with a colorimetric method. For the analysis of the results we have used the non-parametric Wilcoxon Signed Ranks test.

Results. There were 15 women and the mean (± SD) age and duration of diabetes were 59.39 (± 7.92) and 9.46 ± 6.19 yr respectively. Mean (±SD) HbA1c at enrolment was 7.77 ± 1.18 %. The mean (±SD) value of fructosamine decreased significantly from 568.14 (±190.67) μmol/L to 467.10 (±126.98) μmol/L ($p < 0.0001$). The mean decrease between the first and second measurement was 17.8%, 101.03 (±132.17) μmol/L in absolute term.

Conclusions. Decrease in fructosamine concentration can be described at least as a "positive side effect" of ALA used for the treatment of the painful peripheral diabetic neuropathy. As far as we know there is only one study that used fructosamine as a criterion for evaluating the safety and tolerability of orally administred ALA in patients with type 2 diabetes.

Key words. type 2 diabetes, alpha-lipoic acid, fructosamine, peripheral neuropathy, antioxidants.

INTRODUCTION

In the past years several studies suggested that alpha-lipoic acid (ALA) can have positive effects on glucose metabolism by enhancing glucose disposal in patients with type 2 diabetes (1), improving glucose uptake through intracellular

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glucose transporter redistribution in cultured adipocytes (2), activating insulin receptors in isolated soleus muscles in rats ("an insulin-mimicking property") (3,4) and improving insulin sensitivity in patients with type-2 diabetes, evaluated through the hyper-insulinemic euglycemic clamp technique (5). A study in which fructosamine was used as a criterion for evaluating the safety and tolerability of orally administrated ALA in patients with type 2 diabetes (6) was a subject of intense criticism due to the pharmacologic form of ALA ("controlled-release lipoic acid") used (7,8).

Alpha-lipoic acid (ALA) is used as a prescription drug for treatment of diabetic neuropathy in Central and Eastern Europe countries. This indication is sustained by the results of several randomized placebo-controlled studies in patients with symptomatic peripheral diabetic neuropathy (9-13), with cardiac autonomic neuropathy (14) and a meta-analysis of these studies (15). The ALA is known mainly as a naturally occurring antioxidant, that acts as a scavenger for reactive oxygen and nitrogen species (16), regenerator for other antioxidants (vitamin C, glutathione, and alpha-tocopherol) (17) and chelator of free metal ions with oxidative action (18). In a recently published study (19) it was also demonstrated that a fixed combination of benfotiamine and slow-release oral ALA has positive effects on markers of reactive oxygen-induced pathways of complications in patients with type 1 diabetes.

The aim of this study was to evaluate, in an open-label, non-randomized study, in usual ambulatory settings, the effect of short term (two weeks) intravenous ALA infusion (Thiogamma®, Wörwag Pharma GmbH, Germany) on fructosamine level, in patients with type 2 diabetes and painful peripheral diabetic neuropathy after the failure of at least four weeks of treatment with simple analgetics (acetaminophen).

PATIENTS AND METHODS

Twenty-eight consecutive patients were studied, having as inclusion criterion the diagnosis of type 2 diabetes, an established diagnosis of painful peripheral diabetic neuropathy with at least four weeks history of unsuccessful usual analgesic treatment, a score of at least 3 on visual numeric pain scale (VNS) (max 10), HbA1c lower than 10% and a written informed consent. All these criteria represent, in our protocols, indications for the initiation of parenteral and subsequently oral ALA treatment.

The patients received 10 daily infusions of 600 mg ALA in 300 mL of normal saline, infused over 30 min. The diabetes treatment regimen was not changed during this period, there were no changes in the insulin doses either. Acetaminophen was used on demand. Fructosamine was measured in fasting state, using a colorimetric method with photometric endpoint (Hospitex Diagnostics s.r.l. - Italy) in the first and last day of infusions. We have used the SPSS 10 package for descriptive statistics and the results were analyzed using the non-parametric Wilcoxon Signed Ranks test and Spearman's 2-tailed correlation test.

RESULTS

The group had the characteristics of a long duration type 2 diabetes, the majority having abdominal obesity and being treated with insulin, either as monotherapy or in combination with oral drugs (Table 1).

Table 1. The demographic and clinical characteristics of patients

Characteristics	
Number of cases	28
Gender (males/females)	13/15
Diabetes duration (yr)	9.46 ± 6.19
BMI (kg/m^2)	31.02 ±4.75
Waist circumference (cm)	
men	102.54±13.73
women	104.67±14.00
Diabetes treatment (n)	4
Insulin alone	11
Insulin + oral	6
Oral	11
HbA1c (%) (limits)	7.77 ± 1.18 (5.40-9.90)

The patients tolerated well the infusions, without any drug-related or procedure-related side effects. The intensity of pain (evaluated on the first and the last day with the VNS) decreased in 27 of the patients from a mean (±SD), of 6.95 (±1.84) to 2.57 (±1.75) after ten days ($p < 0.0001$) (Table 2). One patient scored the same value in the beginning and at the end. The mean (±SD) of fasting glycemia on the last day of infusions was 158.79 (±50.78) mg/dL, significantly ($p= 0.005$) lower than that from beginning, 179.93 (±49.75) mg/dL. In 25 patients the value of fructosamine decreased and in three increased. Overall the mean (±SD) value of fructosamine decreased significantly from 568.14 (±190.67) µmol/L to 467.10 (±126.98) µmol/L ($p < 0.0001$). In three patients the final value was lower than 285 µmol/L, the "non diabetic" value recommended by the producer (Table 2).

The mean (±SD) of differences between the first and second measurements was 101.03 (±132.17) µmol/L and had a negative correlation with age ($r = - 0.414$, $p = 0.028$), a not significant negative correlation with diabetes duration ($r = - 0.145$, $p = 0.46$) and a positive not significant correlation with HbA1c ($r = 0.265$, $p = 0.17$).

Table 2. Comparison of analyzed parameters

Parameter	Initial	After 12 days	p
Pain score, mean (95% CI)	6.95 (6.23-7.66)	2.57 (1.89-3.25)	< 0.0001
Fasting glycemia, mg/dL, mean (±SD)	179.93 (49.75)	158.79 (50.78)	0.005
Fructosamine, µmol/L, mean (95% CI)	568.14 (494.20-642.08)	467.10 (417.86-516.34)	< 0.0001

CI- confidence interval; p significant at the level < 0.05

DISCUSSION

Our intention was to evaluate the effects of intravenous ALA administration on fructosamine concentration, a still underused indicator of short time (2-3 weeks) glycemic control, in patients with painful DPN. This intention was inspired by the recent communications on modest but significant increase of fasting glycemia and HbA1c for duloxetine (20) and "clinical meaningful increase of body weight" for gabapentin (21) and pregabalin (22), all FDA approved drugs for the treatment of DPN. This kind of "small side effects" can have, after the "rosiglitazone story" (23), another perspective.

The effects of ALA on glucose metabolism continue to be a matter of debate. It is even more difficult to speculate on the relevance of these effects for clinical practice. In a recent review on ALA supplementation (24), after evaluating the results of one of the above mentioned study (1) the authors made the assumption that "if the reported increases in metabolic clearance rate and insulin sensitivity were to persist with continued ALA therapy, then its effect can be compared favorably with metformin, a widely prescribed medication that increases insulin sensitivity and glucose utilization in diabetes".

In the Sydney study (13) the administration of 14 infusions with 600 mg of ALA during 4 weeks (first week was a run-in phase and only placebo was infused) produced a significant 0.22% decrease of HbA1c, but in a comparable study (12) the decrease of HbA1c after 19 days was not significant, from 8.5 ± 0.2% to 8.3 ± 0.2% in the ALA arm and from 8.7 ±0.1% to 8.3 ± 0.1% in the placebo arm. In the only study in which fructosamine was used as a criterion for evaluating the safety and tolerability of orally administrated ALA in patients with type 2 diabetes, the mean plasma fructosamine concentration was reduced from 313 to 283 micromol/L($p<0.05$) after 12 weeks of orall treatment with "controlled-release lipoic acid".

In conclusion, the 17.78% decrease in fructosamine concentration in our study can be described at least as a "positive side effect" of intravenous 600 mg ALA infusion for treatment of painful DPN. The magnitude of fructosamine decrease was significantly higher in younger patients and not significantly correlated with duration of diabetes and HbA1c.

We do not intend to speculate on this finding due to the non-randomized design of the study. We have to underline that these results were obtained in a non-randomized, uncontrolled design study, with a relatively small number of subjects.

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