

PHARMACOKINETICS, TOLERABILITY, AND FRUCTOSAMINE-LOWERING EFFECT OF A NOVEL, CONTROLLED-RELEASE FORMULATION OF α -LIPOIC ACID

Joseph L. Evans, PhD,^{1*} Catherine J. Heymann, PA-C,² Ira D. Goldfine, MD,³
and Laurence A. Gavin, MD^{2,3}

ABSTRACT

Objective: To determine the pharmacokinetics, safety, and tolerability of a novel, controlled-release oral formulation of α -lipoic acid (LA) and to investigate whether sustaining the concentration of LA in plasma would have a beneficial effect on glycemic control in patients with type 2 diabetes.

Methods: For the pharmacokinetic study, a single, 600-mg dose of either controlled-release LA (CRLA) or quick-release LA (QRLA) was administered orally to 12 normal human subjects. The plasma profile of LA was determined for 24 hours after administration of the dose, and pharmacokinetic analyses were performed. For the safety and tolerability study, 21 patients with type 2 diabetes were given 900 mg of CRLA daily for 6 weeks, followed by 1,200 mg of CRLA daily for an additional 6 weeks. Active treatment was followed by a 3-week washout period. Throughout the study, patients continued to take their prestudy antidiabetic medications, which included metformin (Glucophage), sulfonylureas (Amaryl, glyburide, and Glucotrol), acarbose (Precose), troglitazone (Rezulin), and insulin (either as monotherapy or in combination). CRLA was evaluated for safety and tolerability as well as for effects on glycemic control.

Results: The T_{\max} (time to maximal plasma concentration) of LA administered as CRLA was 1.25 hours and was approximately 2.5-fold longer in comparison with the T_{\max} for QRLA ($T_{\max} = 0.5$ hour; $P < 0.02$). No severe side effects or changes in either liver or kidney function or hematologic profiles were noted after the administration of CRLA. In 15 patients, the mean plasma fructosamine

concentration was reduced from 313 to 283 $\mu\text{mol/L}$ ($P < 0.05$) after 12 weeks of treatment with CRLA.

Conclusion: CRLA increased the plasma concentration of LA over time in healthy subjects, and CRLA was safe, well tolerated, and effective in reducing plasma fructosamine in patients with type 2 diabetes. (**Endocr Pract.** 2002;8:29-35)

Abbreviations:

ANOVA = analysis of variance; AUC = area under the plasma concentration-time curve; C_{\max} = maximal observed plasma concentration; CRLA = controlled-release α -lipoic acid; HbA_{1c} = glycated hemoglobin; LA = α -lipoic acid; QRLA = quick-release α -lipoic acid; $T_{1/2}$ = terminal phase elimination half-life; T_{\max} = time to maximal plasma concentration

INTRODUCTION

α -Lipoic acid (LA) is an eight-carbon fatty acid that is synthesized in trace quantities in organisms ranging from bacteria to humans (1-3). LA functions naturally as a cofactor in several mitochondrial enzyme complexes responsible for oxidative glucose metabolism and cellular energy production (4,5). When administered exogenously, LA and its reduced form, dihydrolipoic acid, act as multifunctional antioxidants (1,2). LA has been prescribed in Germany for more than 30 years for the treatment of diabetes-induced neuropathy (6-8), and results from several recent controlled clinical studies indicate that this compound is safe, well tolerated, and efficacious (8).

In addition to the beneficial effects of LA on diabetes-induced neuropathy, several clinical studies have shown an improvement in insulin sensitivity and whole-body glucose metabolism in patients with type 2 diabetes after continuous intravenous infusion of LA (9-11). Investigators have reported that intravenous infusion of LA substantially increases insulin-mediated glucose disposal (~30 to 50%) (9,10), whereas oral administration of LA has only marginal effects (<20%) (12,13). Furthermore, the currently available oral forms of LA have not been reported to reduce glucose, fructosamine, or glycated hemoglobin

Submitted for publication February 2, 2001

Accepted for publication June 15, 2001

From the ¹Medical Research Institute, San Bruno, California, ²Northern California Diabetes Institute, Seton Medical Center, Daly City, California, and ³Diabetes Research Laboratory, Mount Zion Hospital and Department of Medicine, University of California, San Francisco, California.

*Current address: Diabetes Program, Telik, Inc., South San Francisco, California.

Address correspondence and reprint requests to Dr. L. A. Gavin, Northern California Diabetes Institute, Seton Medical Center, 1800 Sullivan Avenue, Suite 408, Daly City, CA 94015.

© 2002 AACE.

(HbA_{1c}) levels in patients with diabetes (12-20). Perhaps this limitation of orally administered LA might be a function of its abbreviated duration in plasma (in comparison with intravenously administered LA), resulting from extensive first-pass metabolism (>50%) and short plasma half-life (<0.5 hour) (21). In this regard, the superior ability of intravenously administered LA to improve insulin sensitivity might be attributable to the achievement of a higher plasma concentration of LA or the maintenance of the concentration for a longer duration. A continuous infusion (during a 20-minute period) of 200 mg of LA resulted in a peak plasma level of approximately 8 µg/mL, and detectable levels were still evident 6 hours after the start of infusion (21). In contrast, oral administration of a 200-mg tablet resulted in a peak plasma level of approximately 0.66 µg/mL, which returned to baseline <3 hours after administration of the tablet (22).

In this preliminary, open-label study, we evaluated the pharmacokinetics, safety, and tolerability of a novel oral formulation of controlled-release LA (CRLA). This formulation was designed to maintain the plasma concentration of LA over time by using controlled-release drug delivery technology (polymeric cellulose resins). In addition, we investigated whether this agent would result in a beneficial effect on glucose control in patients with type 2 diabetes. We found that this agent was safe, well tolerated, and effective in reducing plasma fructosamine levels in patients with type 2 diabetes.

MATERIAL AND METHODS

Subjects and Study Design

Pharmacokinetic Study

The pharmacokinetic profile of CRLA was evaluated in an open-label, single-dose, randomized, two-way crossover design. The study was sponsored by Medical Research Institute (San Bruno, CA; www.lipoic.com) and conducted by Covance Clinical Research Unit at their Madison, WI, study site. Twelve healthy male volunteers received a single dose of two 300-mg tablets of either CRLA (Medical Research Institute) or three 200-mg capsules of quick-release LA (QRLA; Solgar, Leonia, NJ) after an 8-hour overnight fast (23). The study subjects did not eat during the first 4 hours after dosing. Subjects were randomly assigned to either sequence 1 (QRLA then CRLA) or sequence 2 (CRLA then QRLA), with a washout of at least 3 days between treatments. Blood samples for the determination of plasma LA levels were collected through an indwelling catheter at the following times: 0 hour (before the dose); 5, 10, 15, 20, 30, and 45 minutes; and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, and 24 hours after the dose. The concentration of LA in plasma was determined by a validated, high-performance liquid chromatographic assay with use of fluorescence detection (24). The lower limit of quantitation of LA was 15 ng/mL, and the upper limit was 500 ng/mL. Pharmacokinetic analyses of LA were computed by using WinNonlin Professional software (version 3.0, Pharsight,

Inc.). Plasma assays and statistical analyses were performed by Covance Laboratories, Inc. (Madison, WI).

Safety and Tolerability Study

The safety and tolerability of CRLA were assessed along with effects on glycemic control in an open-label, longitudinal design in 21 patients with type 2 diabetes, who acted as their own control. The study was sponsored by Medical Research Institute and conducted by one of us (L.A.G.) within a private practice setting at Seton Medical Center (Daly City, CA). To be included in the study, patients were required to be diagnosed with type 2 diabetes (C peptide >1.2 ng/mL), under adequate control (HbA_{1c} between 7.5 and 10.5%), and with a disease duration <35 years. Patients with a history of cerebrovascular disease, congestive heart failure, advanced nephropathy, diastolic blood pressure >100 mm Hg, or body mass index >35 kg/m² were ineligible for enrollment.

Because this study was intended primarily to assess the safety and tolerability of a new formulation, patients were allowed to continue their prestudy antidiabetic medications concurrently to facilitate patient recruitment. These medications included metformin (Glucophage), sulfonylureas (Amaryl, glyburide, and Glucotrol), acarbose (Precose), troglitazone (Rezulin; now withdrawn from the market), and insulin. No change in dosage of these medications was made during the run-in period or during the course of the study.

The baseline clinical characteristics of the patients are shown in Table 1. The mean HbA_{1c} level was 8.2 ± 1.5%. After a run-in period of 2 weeks, patients received 12 weeks of active treatment of CRLA. The agent was administered as 900 mg daily (two 300-mg tablets 30 minutes before breakfast and one 300-mg tablet 30 minutes before dinner) for 6 weeks, followed by 1,200 mg daily (two 300-mg tablets before breakfast and one 300-mg tablet before both lunch and dinner) for 6 weeks. A 3-week washout period followed active treatment. Patients were monitored on a regular basis for glucose and lipid control, liver enzymes, and other clinical markers, including physical examination, vital signs, and adverse experience queries.

Six patients were not included in the final statistical analyses. These exclusions were made blinded to the results. Four patients were excluded because of their recurring failure (3 instances) to adhere to their allocated diets. Diet was judged initially acceptable if it provided sufficient caloric intake to maintain body weight and the caloric distribution approximated the following: 50 to 60% carbohydrate, <30% fat, and 15 to 20% protein. Diets were evaluated at the beginning of the run-in phase and monitored on a regular basis throughout the study. Failure of dietary adherence was judged to have occurred if carbohydrate, fat, or total caloric intake grossly exceeded (>150%) a patient's usual weekly intake, on the basis of patient interviews. One patient was excluded because of premature withdrawal due to a recurring illness considered unrelated to study medication, and one patient was excluded from analyses because of repeatedly missed laboratory

Table 1
Clinical Characteristics of Study Subjects at Baseline,
During Treatment, and After Treatment*

Characteristics	Baseline	Week 6	Week 12	Week 15 (washout)	Week 12 versus baseline (<i>P</i> value)
Number of subjects	21
Age (yr)	61 ± 11.1
Male, no. (%)	9 (42.9)
Diabetes duration (yr)	11 ± 8.1
Height (inches)	67 ± 4.7
Weight (lb)	195 ± 37.2	199 ± 40.0	193 ± 32.2	197 ± 35.6	-2.4 ± 12.7 (0.60)
Body mass index (kg/m ²)	31.1 ± 4.7	31.2 ± 4.9	30.2 ± 4.6	30.9 ± 4.8	-0.9 ± 2.8 (0.35)
HbA _{1c} (%)	8.2 ± 1.5	8.4 ± 0.6	8.2 ± 0.8	8.0 ± 0.7	0.03 ± 0.4 (0.94)
Fructosamine (μmol/L)	313 ± 48.6	307 ± 43.0	283 ± 48.7†	304 ± 56.8	-30.1 ± 9.7 (0.05)
Fasting glucose (mg/dL)	157 ± 34.0	174 ± 41.4	168 ± 36.5	150 ± 46.9	10.4 ± 11.3 (0.37)
Fasting C peptide (ng/mL)	5.0 ± 3.8	4.6 ± 2.7	4.2 ± 2.8	5.0 ± 3.2	-0.84 ± 0.7 (0.26)
Triglycerides (mg/dL)	222 ± 109	213 ± 123	218 ± 124	240 ± 164	-4.4 ± 20.5 (0.84)
Cholesterol (mg/dL)	180 ± 42.6	185 ± 29.5	187 ± 33.9	190 ± 35.7	6.4 ± 7.7 (0.42)
HDL cholesterol (mg/dL)	43.4 ± 9.2	43.2 ± 10.8	41.9 ± 8.2	46.3 ± 11.6	-1.57 ± 1.7 (0.38)
LDL cholesterol (mg/dL)	94.5 ± 38.5	103 ± 30.1	105 ± 34.3	101 ± 40	10.9 ± 5.7 (0.08)
VLDL cholesterol (mg/dL)	41 ± 18.2	34.3 ± 14.0	38.8 ± 17.3	38.7 ± 21.4	-2.23 ± 4.2 (0.60)
Blood pressure (mm Hg)					
Systolic	123 ± 11.1	122 ± 16.0	128 ± 14.7	134 ± 19.7	4.27 ± 3.6 (0.26)
Diastolic	74.1 ± 7.3	68.0 ± 9.5	72.3 ± 10.3	73.5 ± 10.0	-1.86 ± 3.0 (0.55)

*HbA_{1c} = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein. Data are shown as mean ± standard deviation, except for week 12 versus baseline, which is mean ± standard error of the mean.

†*P*<0.05 (paired *t* test versus baseline).

determinations. Glucose, HbA_{1c}, clinical chemistry and hematology assays, and lipid panels were performed in the clinical laboratory at Seton Medical Center. Fructosamine and C-peptide assays were performed at Specialty Laboratories, Inc. (Santa Monica, CA). Intra-assay and interassay coefficients of variation were 5%.

Ethics

The protocols for the pharmacokinetic study and the safety and tolerability study were approved by the Institutional Review Boards of Covance and the Seton Medical Center, respectively. For both trials, each subject was informed about the purpose and risks of the study and had given written consent to participate. The studies were conducted in accordance with US Title 21 Code of Federal Regulations commonly known as good clinical practices, which are consistent with the Declaration of Helsinki. CRLA is a commercially available, nonprescription

product (see subsequent section) regulated by the US Dietary Supplement Health and Education Act and did not require investigational new drug approval before the initiation of these clinical studies.

Controlled-Release α-Lipoic Acid

LA used in the formulation of CRLA was purchased from Antibioticos SA (Rodano, Italy). This material is of the highest purity commercially available (>99.0%) and produced in accordance with current good manufacturing practices. CRLA tablets were formulated and manufactured for Medical Research Institute in the United States in accordance with current good manufacturing practices. Since 1999, CRLA has been manufactured and distributed in the United States by Medical Research Institute under the trade name of Glucotize. The proprietary nature of CRLA is protected under US patents #6,191,162 and 6,197,340, and additional patents are pending.

RESULTS

Clinical Trial 1: Pharmacokinetic Study in Healthy Subjects

The mean plasma concentration profile of LA after oral dosing is shown in Figure 1. The median T_{max} (time to maximal plasma concentration) for QRLA was 0.5 hour (range, 0.25 to 1.5), which is indicative of rapid absorption with respect to LA. In comparison, the median T_{max} for CRLA was 1.25 hours (range, 0.5 to 4.5), representing a 2.5-fold increase ($P < 0.02$; analysis of variance [ANOVA]). For C_{max} (maximal observed plasma concentration), mean values (\pm standard deviation) of $6,675 \pm 3,703$ ng/mL and $1,793 \pm 742$ ng/mL were determined for the QRLA and CRLA treatments, respectively ($P < 0.002$; ANOVA). The mean ratio of C_{max} for CRLA treatment to QRLA treatment was 27% and is reflective of the decrease in C_{max} typically observed in controlled-release formulations. The maximal plasma concentration of 1,793 ng/mL achieved by a single-dose administration of 600 mg of CRLA corresponds to approximately 10 μ mol/L. This plasma concentration persisted for approximately 2.5 hours after dosing (Fig. 1). For AUC_{0-24} (area under the plasma concentration-time curve from hours 0 to 24), mean values of $4,466 \pm 1,157$ and $2,621 \pm 385$ ng \cdot h/mL were determined for the QRLA and CRLA treatments, respectively ($P < 0.0001$; ANOVA). The mean ratio of AUC_{0-24} for CRLA treatment to QRLA treatment was $\sim 60\%$ and suggests a reduction in overall bioavailability of the CRLA formulation in comparison with QRLA. The mean terminal elimination half-life ($T_{1/2}$; time required for the concentration in plasma to decline to one-half the initial concentration, or rate of elimination) was 0.5 ± 0.61

hour for QRLA and 0.4 ± 0.22 hour for CRLA ($P < 0.39$). These values were not significantly different, presumably because of high intersubject variability after treatment with QRLA.

Clinical Trial 2: Safety and Tolerability Study in Patients With Type 2 Diabetes

No severe side effects were reported after the administration of CRLA to patients with type 2 diabetes. Two patients described a slight metallic taste after the dose was increased to 1,200 mg/day, but this effect was transient and did not necessitate withdrawal from the study. No significant changes were found in liver enzymes, liver or kidney function, or hematologic profiles (data not shown). Thus, CRLA was well tolerated and safe at daily doses of 900 mg for 6 weeks followed by 1,200 mg for 6 weeks.

CRLA exhibited a significant effect with regard to the reduction of plasma fructosamine concentration. At baseline, the mean plasma fructosamine level (\pm standard error of the mean) was 313 ± 48.6 μ mol/L ($N = 15$); after 6 weeks of treatment, it was 307 ± 43.0 μ mol/L ($P < 0.465$; Fig. 2). At this point, the dosage of CRLA was increased to 1,200 mg/day. After 3 weeks on this higher dose, the mean plasma fructosamine level was reduced to 275 ± 42.6 μ mol/L ($P < 0.033$; Fig. 2). At the completion of active treatment (12 weeks), the mean plasma fructosamine concentration was 283 ± 48.7 μ mol/L ($P < 0.05$; Fig. 2), corresponding to an overall mean decrease from baseline of 30.1 ± 9.7 μ mol/L. After a 3-week washout period, the mean plasma fructosamine level increased to 304 ± 56.8 μ mol/L ($P < 0.454$; Fig. 2). No significant changes were observed in either fasting plasma glucose or HbA_{1c} values. At baseline, mean fasting plasma glucose

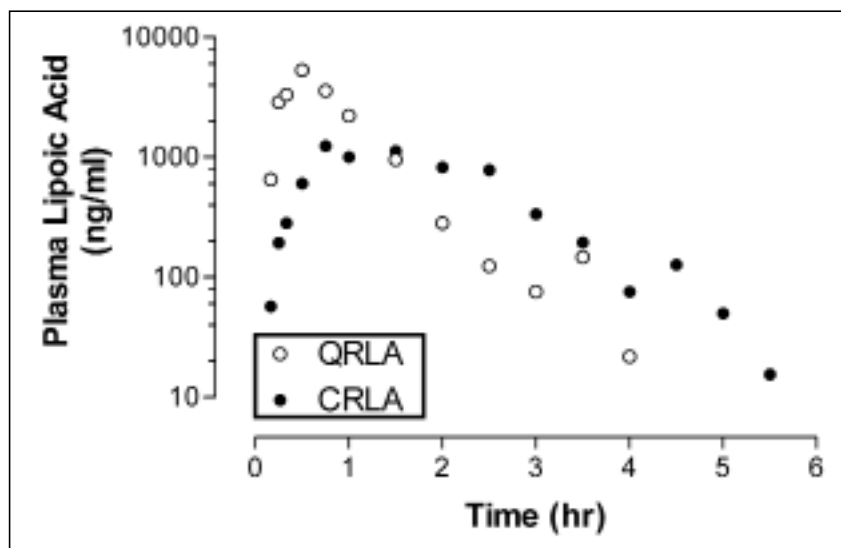


Fig. 1. Mean α -lipoic acid (LA) concentration in plasma after single oral 600-mg dose of quick-release LA (QRLA) and controlled-release LA (CRLA) in 12 healthy study subjects. For each formulation, plasma LA concentration returned to baseline levels by 6 hours. Several data points that correspond to plasma values < 10 ng/mL are not shown in this plot. The statistical evaluation of these data is summarized in the text (see Results—Clinical Trial 1).

and HbA_{1c} were 157 ± 34 mg/dL and $8.2 \pm 1.5\%$, respectively. At the completion of active treatment (12 weeks), mean fasting plasma glucose and HbA_{1c} were 168 ± 36.5 mg/dL ($P < 0.37$) and $8.2 \pm 0.8\%$ ($P < 0.94$), respectively. A trend toward a reduction in C peptide was observed. At baseline, the mean fasting plasma C peptide was 5.0 ± 3.8 ng/mL; after 12 weeks of treatment, it declined to 4.2 ± 2.8 ng/mL (Table 1). The overall mean decrease from baseline was 0.84 ± 0.7 ng/mL ($P < 0.26$). No significant changes were observed in triglycerides, total, high-density lipoprotein, or low-density lipoprotein cholesterol levels, body weight, or body mass index after treatment (Table 1).

DISCUSSION

This is the first report of the development, use, and clinical assessment of a controlled-release formulation of LA. This approach was initiated and pursued to test the hypothesis that limitations of the current oral QRLA formulation with respect to effects on insulin sensitivity and metabolic control (in comparison with intravenous infusion) might be a function of the abbreviated duration for which LA is maintained in plasma.

With use of controlled-release drug delivery technology, the T_{max} of LA was increased approximately 2.5-fold (1.25 hours for CRLA versus 0.5 hour for QRLA), reflecting the slower release of LA from the formulation matrix. Importantly, the plasma concentration of LA remained level for several hours in the controlled-release formulation, whereas it declined more rapidly when delivered in quick-release capsules. The therapeutic implication of maintaining LA in plasma for a longer duration than can be achieved with the typical oral QRLA formulation is

suggested by the clinical benefit of LA on whole-body insulin sensitivity when administered by intravenous infusion (9-11).

CRLA exhibited a decrease in C_{max} in comparison with QRLA. This result is also a formulation effect, inasmuch as controlled-release formulations are designed to reduce C_{max} (25). The reason for the observed decrease in overall bioavailability of the CRLA (judged by a lower AUC) in comparison with QRLA is unknown. The rate or extent of absorption of the two formulations may have differed. It cannot be determined from this study whether the controlled-release matrix constituents affected the absorption of LA. Another possibility is that the slower release of the CRLA may have promoted more extensive first-pass hepatic metabolism. The $T_{1/2}$ value was not significantly different between the two formulations. This finding suggests that the increased duration of CRLA was due to controlled plasma delivery as opposed to a decrease in the actual rate of elimination. The $T_{1/2}$ of the QRLA capsules used in this study is in good agreement with that reported for enteric-coated tablets (21).

At dosages of 900 mg/day for 6 weeks followed by 1,200 mg/day for 6 weeks, CRLA was well tolerated and produced no significant changes in liver enzymes, liver or kidney function, or hematologic profiles. Moreover, no serious side effects were observed. These results are in good agreement with the long history of safety and tolerability of LA, whether administered by intravenous infusion or orally (8). It cannot be determined from this study whether CRLA interacted with other medications, although no study subjects required an adjustment in dose of their concurrent medication. For assessment of the potential for drug-drug interaction between CRLA and

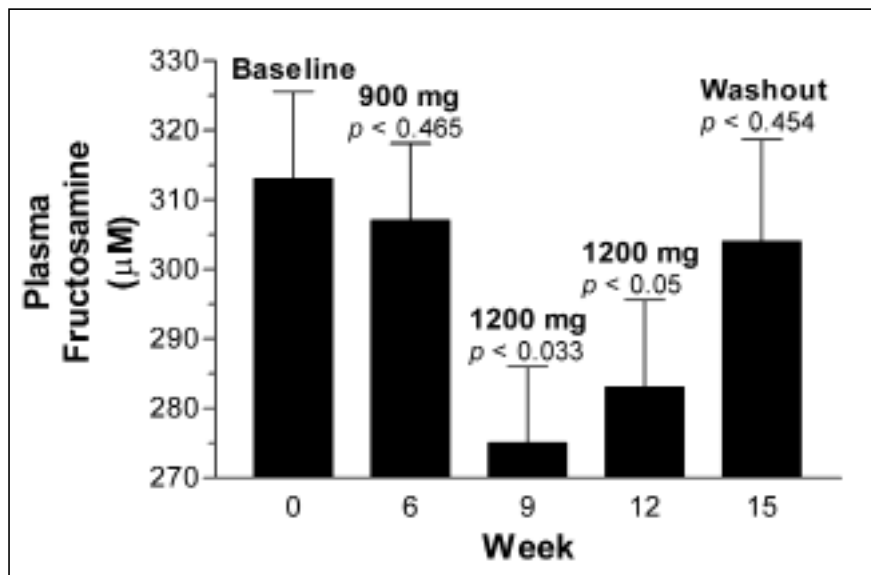


Fig. 2. Effect of controlled-release α -lipoic acid (CRLA) on plasma fructosamine concentrations in patients with type 2 diabetes ($N = 15$) during 12-week period of active treatment and 3-week washout phase. Initial dosage of CRLA was 900 mg/day; dosage was increased to 1,200 mg/day after week 6. P values were determined from paired t test versus baseline. Statistical significance was accepted at $P < 0.05$.

other antidiabetic medications, more systematic studies would be necessary. A recent study found that coadministration of single oral doses of QRLA and glibenclamide, or of QRLA and acarbose, did not result in drug-drug interactions (26).

With respect to glycemic control, CRLA caused a decrease in plasma fructosamine concentration, an effect that was statistically significant at weeks 9 and 12. This timing corresponds to weeks 3 and 6 after dosage escalation to 1,200 mg of CRLA per day. At the completion of active treatment, the decrease in fructosamine from baseline was about 30 $\mu\text{mol/L}$, corresponding to an approximate 10% overall reduction. After a 3-week washout period, the fructosamine concentration increased toward the baseline value. This finding provides preliminary support for our hypothesis that maintaining the level of LA in plasma over time might result in an overall improvement in glycemic control.

The decrease in fructosamine concentration was observed in the absence of a reduction in fasting plasma glucose level. The reason for this result is unknown and will have to be addressed in future studies in which postprandial glucose levels are also determined. The decrease in fructosamine level was also observed in the absence of a reduction in HbA_{1c} value. This outcome might be attributable to the abbreviated duration of treatment at the effective 1,200-mg dose (6 weeks of total exposure) or to a statistical power too limited to detect a significant change—especially in light of the degree of variability of HbA_{1c} at baseline. A larger double-blind, placebo-controlled study of longer duration would be required to address this question.

CONCLUSION

In this preliminary open-label study, CRLA increased the plasma concentration of LA over time in healthy subjects, and CRLA was safe, well tolerated, and effective for significantly reducing plasma fructosamine concentrations in patients with type 2 diabetes. Although encouraging, these preliminary results need to be confirmed in a larger, double-blind, placebo-controlled study in which HbA_{1c} is the primary endpoint. If this goal is achieved, CRLA may emerge as a new, adjunctive, antidiabetic treatment.

DISCLOSURE AND ACKNOWLEDGMENT

Dr. L. A. Gavin was supported by funding from Medical Research Institute (San Bruno, CA), which manufactures and distributes CRLA. Dr. I. D. Goldfine was supported in part by the Jay Gershow Fund and the American Diabetes Association. We are grateful to Dr. Peter Havel (University of CA, Davis) for helpful comments, suggestions, and critical review of the manuscript during its preparation. Statistical analyses of the pharmacokinetic data were expertly performed by Dr. Guhan Balan (Covance, Inc.), and statistical analyses of the safety and metabolic data were expertly performed by Dr. Yu-Kun Chiang (San Jose, CA).

REFERENCES

1. **Packer L, Witt EH, Tritschler HJ.** Alpha-lipoic acid as a biological antioxidant. *Free Radic Biol Med.* 1995;19:227-250.
2. **Packer L, Witt EH, Tritschler HJ.** Antioxidant properties and clinical applications of alpha-lipoic acid and dihydrolipoic acid. In: Cadenas E, Packer L, eds. *Handbook of Antioxidants.* New York: Marcel Dekker, 1998: 545-591.
3. **Fuchs J, Packer L, Zimmer G, eds.** *Lipoic Acid in Health and Disease.* New York: Marcel Dekker, 1997.
4. **Reed LJ, DeBusk BG, Gunsalus IC, Hornberger CS Jr.** Crystalline α -lipoic acid: a catalytic agent associated with pyruvate dehydrogenase. *Science.* 1951;114:93-94.
5. **Biewenga GP, Haenen GR, Bast A.** The pharmacology of the antioxidant lipoic acid. *Gen Pharmacol.* 1997;29:315-331.
6. **Biewenga G, Haenen GR, Bast A.** The role of lipoic acid in the treatment of diabetic polyneuropathy. *Drug Metab Rev.* 1997;29:1025-1054.
7. **Ziegler D, Gries FA.** Alpha-lipoic acid in the treatment of diabetic peripheral and cardiac autonomic neuropathy. *Diabetes.* 1997;46(Suppl 2):S62-S66.
8. **Ziegler D, Reljanovic M, Mehnert H, Gries FA.** Alpha-lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials. *Exp Clin Endocrinol Diabetes.* 1999;107:421-430.
9. **Jacob S, Henriksen EJ, Schiemann AL, et al.** Enhancement of glucose disposal in patients with type 2 diabetes by alpha-lipoic acid. *Arzneimittelforschung.* 1995;45:872-874.
10. **Jacob S, Henriksen EJ, Tritschler HJ, Augustin HJ, Dietze GJ.** Improvement of insulin-stimulated glucose disposal in type 2 diabetes after repeated parenteral administration of thioctic acid. *Exp Clin Endocrinol Diabetes.* 1996;104:284-288.
11. **Evans JL, Goldfine ID.** α -Lipoic acid: a multi-functional antioxidant that improves insulin sensitivity in patients with type 2 diabetes. *Diabetes Tech Ther.* 2000;2:401-413.
12. **Jacob S, Ruus P, Hermann R, et al.** Oral administration of RAC-alpha-lipoic acid modulates insulin sensitivity in patients with type-2 diabetes mellitus: a placebo-controlled pilot trial. *Free Radic Biol Med.* 1999;27:309-314.
13. **Konrad T, Vicini P, Kusterer K, et al.** Alpha-lipoic acid treatment decreases serum lactate and pyruvate concentrations and improves glucose effectiveness in lean and obese patients with type 2 diabetes. *Diabetes Care.* 1999;22:280-287.
14. **Reljanovic M, Reichel G, Rett K, et al.** Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (alpha-lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II); Alpha Lipoic Acid in Diabetic Neuropathy. *Free Radic Res.* 1999;31:171-179.
15. **Ziegler D, Hanefeld M, Ruhnau KJ, et al (ALADIN III Study Group).** Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study); Alpha-Lipoic Acid in Diabetic Neuropathy. *Diabetes Care.* 1999;22:1296-1301.
16. **Ziegler D, Schatz H, Conrad F, Gries FA, Ulrich H, Reichel G.** Effects of treatment with the antioxidant alpha-lipoic acid on cardiac autonomic neuropathy in NIDDM patients: a 4-month randomized controlled multicenter trial (DEKAN Study); Deutsche Kardiale Autonome Neuropathie. *Diabetes Care.* 1997;20:369-373.

17. **Ruhnau KJ, Meissner HP, Finn JR, et al.** Effects of 3-week oral treatment with the antioxidant thioctic acid (alpha-lipoic acid) in symptomatic diabetic polyneuropathy. *Diabet Med.* 1999;16:1040-1043.
18. **Borcea V, Nourooz-Zadeh J, Wolff SP, et al.** Alpha-lipoic acid decreases oxidative stress even in diabetic patients with poor glycemic control and albuminuria. *Free Radic Biol Med.* 1999;26:1495-1500.
19. **Androne L, Gavan NA, Veresiu IA, Orasan R.** In vivo effect of lipoic acid on lipid peroxidation in patients with diabetic neuropathy. *In Vivo.* 2000;14:327-330.
20. **Haak E, Usadel KH, Kusterer K, et al.** Effects of alpha-lipoic acid on microcirculation in patients with peripheral diabetic neuropathy. *Exp Clin Endocrinol Diabetes.* 2000;108:168-174.
21. **Hermann R, Niebch G, Borbe HO, et al.** Enantioselective pharmacokinetics and bioavailability of different racemic alpha-lipoic formulations in healthy volunteers. *Eur J Pharm Sci.* 1996;4:167-174.
22. **Teichert J, Kern J, Tritschler HJ, Ulrich H, Preiss R.** Investigations on the pharmacokinetics of alpha-lipoic acid in healthy volunteers. *Int J Clin Pharmacol Ther.* 1998;36:625-628.
23. **Gleiter CH, Schug BS, Hermann R, Elze M, Blume HH, Gundert-Remy U.** Influence of food intake on the bioavailability of thioctic acid enantiomers. *Eur J Clin Pharmacol.* 1996;50:513-514.
24. **Niebch G, Buchele B, Blome J, et al.** Enantioselective high-performance liquid chromatography assay of (+)R- and (-)S-alpha-lipoic acid in human plasma. *Chirality.* 1997;9:32-36.
25. **Fix J.** Oral drug delivery. In: Mathiowitz E, ed. *Encyclopedia of Controlled Drug Delivery.* Vol 2. New York: John Wiley & Sons, 1999: 698-728.
26. **Gleiter CH, Schreeb KH, Freudenthaler S, et al.** Lack of interaction between thioctic acid, glibenclamide and acarbose. *Br J Clin Pharmacol.* 1999;48:819-825.