



## Technical Report

# Time-Release Lipoic Acid: More Marketing than Data

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## Time-Release Liponic Acid: More Marketing than Data

The role of lipoic acid in clinical practice has been well studied and is backed by a wealth of understanding from *in vitro* and animal studies. Most clinical trials, up to this point, have employed the use of the all-racemic form of lipoic acid (R,S) in intravenous or oral administration. In the past several years, a form of controlled-released lipoic acid (CRLA) has been manufactured and tested in humans, with the assumption that the efficacy of lipoic acid could be improved by slowing the absorption and keeping blood levels of lipoic acid above baseline for longer periods after ingestion. This hypothesis was based on the fact that most studies using lipoic acid (so-called quick release forms- QRLA) do not statistically alter fasting blood glucose or glycated hemoglobin levels (HbA1c) in diabetic individuals. The first test of this hypothesis was published in the January/February 2002 issue of *Endocrine Practice*;<sup>1</sup> where the results of both a pharmacokinetic profile of controlled-release lipoic acid was compared to standard “quick-release” lipoic acid, as well as an uncontrolled safety and tolerability study of controlled-release lipoic acid in type II diabetic patients were described. The conclusions derived from data contained within this 2002 article are being used to promote the sale of controlled-release lipoic acid as a superior form of lipoic acid for clinical practice. We contend that these promotions are misleading, based on the data presented, and have resulted in confusion as to the potential role of lipoic acid in clinical practice. We present here a critique of the article by Evans et al.,<sup>1</sup> as well as a discussion about the general hypothesis concerning the efficacy of lipoic acid.

### 1. Controlled-Release Lipoic Acid dramatically *lowers* absorption by more than 40%

While the abstract of the Evans et al. paper mentions the change in T<sub>max</sub> (the time to maximal plasma concentration), it fails to disclose that the plasma concentration at that maximum (C<sub>max</sub>) was 45% lower in individuals taking the controlled-release lipoic acid compared to those taking the quick-release form. Additionally, the total absorption, based upon the area under the curve (AUC 0-24 hours), was reduced by 42%.

While these numbers are quite significant, the authors say in their discussion “*The reason for the observed decrease in overall bioavailability of the CRLA (judged by a lower AUC) in comparison with QRLA is unknown.*” Those relying on a brief glance at Figure 1 of Evans et al. would not notice such a dramatic difference in bioavailability because the authors chose to display their data using a logarithmic scale, which dramatically alters the ability to see this nearly two-fold difference in bioavailability.

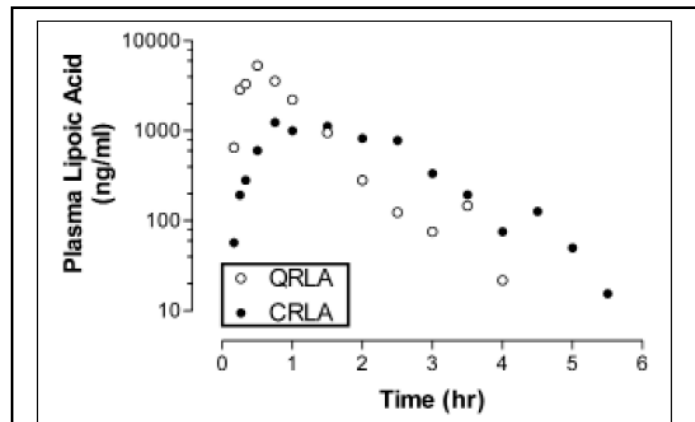


Fig. 1. Mean  $\alpha$ -lipoic acid (LA) concentration in plasma after single oral 600-mg dose of quick-release LA (QRLA) and controlled-release LA (CRLA) in 12 healthy study subjects. For each formulation, plasma LA concentration returned to baseline levels by 6 hours. Several data points that correspond 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).

Original Figure 1 from Evans et al. Copyright 2002 American Association of Clinical Endocrinology- Note the use of logarithmic scale.

## 2. Controlled-Release Lipoic Acid *did not* alter fasting blood glucose or HbA1c.

Again, while the abstract and figure 2 of the Evans et al. paper emphasize the change in fructosamine levels in diabetic patients taking CRLA, absent from the abstract and conclusion were the mention that no changes were seen in fasting blood glucose, HbA1c or serum triglycerides- other important markers for improved glucose control. The authors state (in their discussion) that the reason for the lack of observed change in either the fasting plasma glucose levels or HbA1c is unknown and needs to be explored in future studies. Ironically, it is this very observation with previous lipoic acid studies that prompted this line of research in the first place.

Several other observations need to be made to place this data in context. While the fructosamine changes observed in these type 2 diabetic patients reached the limit of statistical significance ( $p=0.05$ ), these patients continued to take the oral hypoglycemic medications (or insulin) without changes throughout the trial. Although the authors consider this to be an open-labeled “controlled-trial” (patients’ baseline numbers acting as their own controls), enrolling subjects in a trial such as this is likely to increase compliance with either drug or dietary protocols. These changes in behavior could have easily accounted for such modest changes in fructosamine levels, and without a control arm, no conclusion should be drawn from these modest changes. The employment of a 2-week run-in phase to enhance the “self-control” aspect of the trial is still inadequate to control for these lifestyle changes, as fructosamine levels may take a minimum of 2 weeks to readjust. Additionally, 4 patients were excluded from final statistical analysis for recurrent failure to adhere to the allocated diet (>150% caloric intake compared to normal diet). While Evans et al. showed that CRLA was safe and tolerated at the doses used, no evidence of efficacy can be concluded from the data presented.

## 3. Conclusion from Evans et al.

We agree with Evans et al. in their opinion that further studies are needed to determine the potential role of controlled-release lipoic acid in clinical use.<sup>a</sup> We disagree, however, that the data presented shows any clinical benefit in patients consuming CRLA, especially compared to QRLA. Not only did the CRLA have a significantly lower bioavailability than standard lipoic acid (point 1, above), the CRLA tablets were unable to change classic blood glucose parameters such as fasting plasma glucose or HbA1c (point 2). Furthermore, the clinical significance of the fructose-lowering effects of CRLA in this study is difficult to assess since: 1) patients continued on other hypoglycemic therapies, 2) the run-in phase was too short to eliminate potential alterations in diet and drug compliance, 3) no comparison to fructosamine-lowering effects of standard lipoic acid therapies are available (including in this paper since no placebo or QRLA control arms were used).

As of this writing, we are not aware of any other clinical studies that have been published using CRLA in humans.<sup>b</sup> However, in the past 5 years several clinical studies have confirmed the positive benefits of oral lipoic acid (racemic, “quick-release”) in a variety of patients with glucose regulation issues (See Point 4, below). Without additional clinical data to assess controlled-released forms of lipoic acid, and its limited availability as a single active ingredient

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<sup>a</sup> Another sustained release form of lipoic acid has been produced and tested by a German pharmaceutical company. They have not published any data comparing this form with quick-release forms.<sup>2,3</sup> We are not sure if this form is commercially available in the U.S.

<sup>b</sup> A list of apparently on-going pre-clinical trials is listed on the manufacturer’s website ([www.nutravene.com](http://www.nutravene.com)). None of these seem to be designed to compare CRLA with QRLA.

tablet (CRLA tablets requires special processing with ethyl acrylate and beta-cyclodextrin or chitosan), there is little evidence to recommend controlled-release/time-release lipoic acid at this time.

#### 4. Other oral lipoic acid studies confirm positive benefits

Since 2002, several studies have confirmed the use of all-racemic lipoic acid (standard-“quick-release”) in human clinical trials. This section will outline a few of the more important studies related to patients with glycemic-control conditions. For a brief discussion of R-lipoic vs. racemic-lipoic acid, see point 5 below.

Perhaps the longest and most consistent use of lipoic acid in diabetic patients is for the treatment of diabetic polyneuropathy. The original studies typically delivered 600 mg/day of all-racemic lipoic acid, *intravenously*, over 30 minutes. A recent meta-analysis provides evidence that clinically meaningful improvements can be achieved in 3 weeks of such i.v. treatments.<sup>4</sup> Daily intravenous treatments; however, are not as easy to maintain for long periods of time when compared to oral therapy. In a four-arm, randomized placebo-controlled trial, researchers from the most successful i.v. lipoic acid study (the SYDNEY Trial)<sup>5</sup> performed a dose-response study using once per day oral doses of lipoic acid (600mg, 1200 mg, 1800 mg or placebo) in 181 patients with diabetic neuropathy (SYDNEY 2 Trial).<sup>6</sup> They found that 600 mg, once per day, improved neuropathic symptoms and deficits in 5 weeks in patients with diabetic neuropathy. Doses of 1200 mg or 1800 mg proved no better after the first week and were accompanied by additional side-effects. Total symptoms scores (TSS) in the 600 mg oral group dropped an average of 51% ( $9.44 \pm 1.86$  baseline TSS), this compares well to the 52.7% average decrease in TSS scores from the pooled data taken from the 4 well-controlled i.v. studies.<sup>4</sup> This data suggests that oral lipoic acid, in doses similar to i.v. therapy, had similar therapeutic benefits for polyneuropathy and was not dramatically altered by reduced bioavailability.

In a recent open-label trial, 12 diabetic patients with stable blood glucose and HbA1c levels (all managed by metformin), were given 600 mg oral racemic lipoic acid, twice daily (1200 mg/day).<sup>7</sup> Insulin sensitivity was measured by glucose clamp analysis at baseline and after 4 weeks of lipoic acid therapy. Lipoic acid significantly improved glucose utilization as measured by glucose metabolism (M, 85.9% improvement) and insulin sensitivity index (ISI, 63% improvement) in these diabetic patients. These improvements in insulin sensitivity are substantial, resulting in comparable glucose disposal rates to normal healthy controls. No statistical changes in fasting glucose or insulin were observed, and measurements of HbA1c and fructosamine levels were not reported (inclusion criteria required stable metformin-controlled blood glucose prior to study). These data also compare favorably to previous studies using i.v. administration.<sup>8,9</sup>

Furthermore, the modest oral dose of 300 mg/day of oral lipoic acid (racemic) in metabolic syndrome patients statistically improved endothelial function (measured by flow-mediated dilation), while decreasing the pro-inflammatory markers IL-6 and PAI-1 (plasminogen activator inhibitor-1).<sup>10</sup> Other positive clinical trials have also been reported using oral, racemic “quick-release” lipoic acid for a variety of other health conditions in recent years.<sup>11,12,13,14</sup> These data suggest that standard forms of lipoic acid do not suffer appreciable declines in clinical efficacy when used orally, compared to similar doses delivered intravenously and are currently the standard form in clinical experimentation and practice. The apparent lack of statistical changes in fasting blood glucose and HbA1c observed in patients taking a variety of oral and

intravenous doses of lipoic acid, even while improvements in other markers of glucose control are noted, needs to be explored in future studies.

## 5. What about R-lipoic Acid?

Those familiar with the research on alpha-lipoic acid know that cell culture and animal research suggests that the R-form of lipoic acid may have benefits over racemic blend (50:50 blend of R:S lipoic acids). While this subject is beyond the scope of this paper, we will make a few brief comments.

First, while there is abundant clinical research on the racemic form of lipoic acid, we are not aware of any published clinical trials, in humans, using R-lipoic acid; or any comparing R-lipoic acid with the RS-form. Second, since the R-form is derived by separating the two enantiomers, it is much more expensive than the racemic mixture. Without clinical data to suggest the effective equivalent dose, it seems premature to suggest the wide use of R-lipoic acid in clinical practice, and difficult to justify its use from a cost-effectiveness stand-point. Until future studies are performed and/or technological advances reduce the cost of R-lipoic acid, the use of racemic alpha-lipoic acid seems to be the most cost-effective choice at this time.

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