Plasma pharmacokinetics of R-(+)-lipoic acid administered as sodium R-(+)-Lipoate to healthy human subjects

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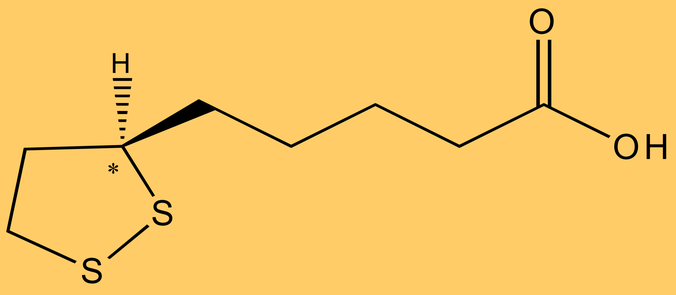

R-(+)-lipoic acid
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Background & Introduction

Alkali metal salts of (RS)-lipoic acid (rac-LA) have been used to improve the aqueous solubility of LA for use in a variety of models.

In vitro and animal models of aging and age-related diseases have demonstrated efficacy for the oral solutions of rac-LA salts in normalizing age-related changes to those of young animals.

Previous studies have demonstrated the superiority of R-(+)-lipoic acid (RLA), the naturally occurring enantiomer over rac-LA. Despite this, RLA pharmacokinetics (PK) is not fully characterized in humans. It is unknown whether the concentrations utilized in the animal and *in vitro* models can be achieved in humans.

RLA is relatively unstable due to its tendency to polymerize, and suffers poor aqueous solubility.

Herein, we present PK data for the 600 mg oral dosing of 12 healthy adult human subjects with the highly bio-available water-soluble, NaRLA. In addition, we tested the effect of a 3x dose on a single subject relative to a 1x dose in the same subject.

Materials and Methods

R-Lipoic Acid Administration:
Subjects consumed 600 mg (total RLA equivalent) of the sodium salts of RLA dissolved in 200 mL of water.

Plasma Extraction:
RLA standards were spiked into each subjects baseline plasma sample at various concentrations (0.5-50 ug/mL) to create standard curves. Appropriate dilution of the RLA working stocks were made in low-alcohol (ethanol final concentration <0.1%) phosphate-buffered saline (PBS) solution to prevent ethanol-induced extraction artifacts. RLA was extracted from samples and plasma spikes with mobile phase. Extraction efficiency of RLA spiked into baseline plasma samples ranged from 84-96% . Baseline plasma spike-extraction sample sets were made for each individual and were used to quantify RLA in the unknown plasma samples of each subjects.

Chromatography:
Analytical determination of RLA was adapted from Sen *et al*. RLA was separated on C18 analytical columns (4.6 X 250 mm) at ambient temperature (MP: 50 mM phosphate buffer:acetonitrile:methanol [50:30:20], pH 2.7, flow: 1 mL/min). RLA was detected with an ESA Coulochem II (ESA, Inc; Chelmsford, MA; guard cell: 0.90 mV; E1: 0.40 mV; E2:0.85 mV.

Pharmacokinetic Analysis:
Plasma PK parameters were determined using PK Solutions software (Montrose, CO), which estimates PK parameters using non-compartmental analysis. The AUC was calculated by PK Solutions using trapezoidal summation and is a representation of the relative bioavailability of the analyte. The plasma half-life (T 1/2) of the terminal elimination phase was calculated based on the data from Tmax to the last quantifiable time point.

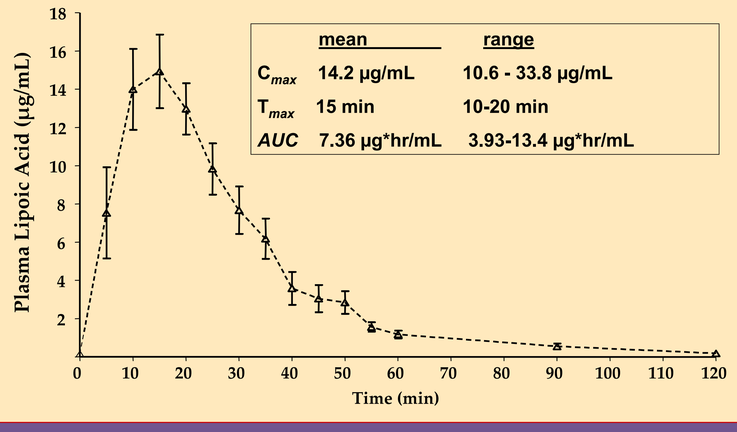

Figure 2: Plasma pharmacokinetics for all subjects (n=12). Data shown are averaged plasma RLA values for each time point in the study.

subj. #	gender	BMI	Cmax (ug/mL)	Tmax (min)	AUC (ug*min/mL)	AUC (ug*hr/mL)	Elimination phase t1/2 (min)
1	m	31	18	15	508.4	8.47	16.6
2	f	24	14.7	10	438.5	7.31	17.7
3	m	28	12.9	15	376.2	6.27	15.7
4	f	20	16.1	10	350.9	5.85	5.2
5	m	26	12.2	15	406.3	6.77	13.6
6	m	24	33.8	10	804.1	13.40	9.6
7	m	20	13.6	10	350.4	5.84	13.3
8	f	22	15.2	20	452	7.53	13.2
9	m	24	21	20	684.1	11.40	11.8
10	m	21	13.3	20	395.4	6.59	11.3
11	m	23	11	15	297.2	4.95	15.7
12	f	18	10.6	10	235.6	3.93	24.1
PK parameter stats:							
		Mean	**16.03**	**14.17**	**441.59**	**7.36**	**14.0**
		Median	14.15	15.00	400.85	6.68	13.5
		SD	*6.32*	*4.2*	*160.2*	*2.67*	*4.66*

Table 1: Pharmacokinetic parameters of 600 mg oral dose R-lipoic acid sodium salt (based on RLA content) in human subjects.

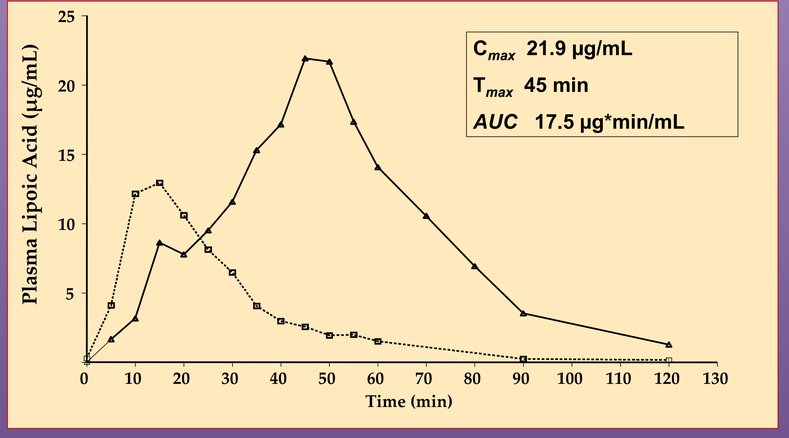

Figure 3: Plasma pharmacokinetics for a single subject (subject 3) given three sequential 600 mg doses at t= 0, 15, 30 min. The individual's single (600 mg) dose PK curve is presented for comparison (dashed line). A two week washout period lapsed between the two dose regimens.

Results

NaRLA displays mean Cmax and AUC values of 16.03 ug /mL and 7.36 ug hr/mL and decreased time to maximum concentration (Tmax) and T1/2 values relative to literature values for RLA or rac-LA.

In order to significantly extend Cmax and AUC, it is possible to administer three 600-mg RLA doses (as NaRLA) at 15-minute intervals to achieve plasma concentrations similar to those from a slow (20-minute) IV infusion of LA.

Conclusions

The poor physical stability, low absorption and bioavailability of free acid preparations of RLA limits its potential pharmaceutical and nutraceutical applications. These limitations are overcome by administering RLA in the form of a salt. The human Cmax and AUC values of RLA are significantly greater than either free acid forms of rac-LA or rac-LA administered as oral solutions of the sodium salts. The fast T 1/ 2 and T max values of RLA indicates a possible stereoselective transport mechanism, favored when SLA is absent. The mean AUC for 600 mg intravenous rac-LA is 12.25 ug hr/mL (Teichert & Preiss 2008) and 7.68 ug hr/mL for the per oral solution of NaRLA, indicating the absolute bioavailability of NaRLA is 62.7%. Rac-LA (600 mg) has been shown to be therapeutically effective. Herein, we demonstrate that it is possible to achieve similar PK profiles and tissue levels with 150 mg of the natural and eutomeric form, RLA when administered as an aqueous solution of NaRLA. NaRLA is the most bioavailable oral dosage form of LA reported to date.

Carlson DA, Smith AR, Fischer SJ, Young KL, Packer L. The plasma pharmacokinetics of R-(+)-lipoic acid administered as sodium R-(+)-lipoate to healthy human subjects. Altern Med Rev (2007) 12(4) 343-51.

For further information

Please contact david@geronova.com. More information on this and related projects can be obtained at *www.geronova.com*.