Age and gender dependent bioavailability of R- and R,S-α-lipoic acid: A pilot study

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Abstract

Lipoic acid (LA) shows promise as a beneficial micronutrient toward improving elder health. Studies using old rats show that \((R)-\alpha\)-LA (R-LA) significantly increases low molecular weight antioxidants that otherwise decline with age. Despite this rationale for benefiting human health, little is known about age-associated alterations in absorption characteristics of LA, or whether the commercially available racemic mixture of LA (R,S-LA) is equally as bioavailable as the naturally occurring R-enantiomer. To address these discrepancies, a pilot study was performed to establish which form of LA is most effectively absorbed in older subjects relative to young volunteers. Young adults (average age = 32 years) and older adults (average age = 79 years) each received 500 mg of either R- or R,S-LA. Blood samples were collected for 3 h after supplementation. After a washout period they were given the other chiral form of LA not originally ingested. Results showed that 2 out of 6 elder males exhibited greater maximal plasma LA and area under the curve for the R-form of LA \textit{versus} the racemic mixture. The elder subjects also demonstrated a reduced time to reach maximal plasma LA concentration following R-LA supplementation than for the racemic mixture. In contrast, young males had a tendency for increased bioavailability of R,S-LA. Overall, bioavailability for either LA isoform was much more variable between older subjects compared to young adults. Plasma glutathione levels were not altered during the sampling period. Thus subject age, and potential for varied response, should be considered when determining an LA supplementation regimen.

Keywords

Glutathione; Pharmacokinetics; Lipoic acid

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1. Introduction

Lipoic acid (LA) is a dithiol compound that is synthesized endogenously by nearly all mammals and is a critical cofactor of key oxidative metabolism enzymes [1,2]. Thus, it serves an important role in mitochondrial energy transduction. Though de novo synthesis supplies all the necessary LA needed for intermediary metabolism, it can also be absorbed from the diet. In fact, tissues and cells maintain active systems to transport, utilize, and excrete the natural non-protein-bound R-enantiomer, and there are potentially separate transport mechanisms for S-LA which arises as a by-product of industrial synthesis. Despite differences in the mode of their transport, approximately 20–40% of orally ingested R- or S-LA is absorbed by the gastrointestinal tract [3,4], suggesting that they are both readily bioavailable.

Orally derived LA has unique biochemical activities separate from its normal metabolic role and is under clinical consideration for a host of pathophysiologic insults. LA is a potent biological antioxidant in vitro, a detoxification agent for heavy metals, a diabetes medicine, and has been implicated as a means to improve age-associated cardiovascular, cognitive, and neuro-muscular declines. It is also been shown to be a modulator of various inflammatory signaling pathways through its high reduction potential, which in biological systems is second only to the NAD(P)H/NAD(P)⁺ redox couple [5–15]. Because of its potential to limit the risk for numerous toxicological and pathophysiological insults, which are often accentuated with age, LA is now touted as an adjunct to improve or maintain elder health [16,17]. In fact, LA is widely used by the senior adult population as a nutritional supplement [18]. However, given that aged individuals often have diminished capacity to absorb many dietary vitamins and micronutrients, including vitamins B12 and D [19–21], it is not known whether LA absorption and bioavailability is adversely affected with age, or whether optimal doses must be altered in this age group to achieve maximal health benefits.

Further complicating the characterization of optimal intake for elder subjects, most commercially available LA preparations consist of R,S-LA, while the naturally occurring form used in metabolism is exclusively the R-enantiomer. It is also this former form that has primarily been used to characterize LA pharmacokinetic parameters. In those studies, it is clear that LA is rapidly absorbed where peak plasma levels are achieved between 0.5 and 2 h after an oral dose [5]. Animal studies show that rapid gastrointestinal uptake is followed by an equally rapid clearance, reflecting both transport into tissues as well as glomerular filtration and renal excretion [22]. While primarily accumulating in the liver, heart, and skeletal muscle, LA is also found in most tissues following oral intake. However, despite the characterization of R-LA absorption and metabolism, it is not known whether there are age-associated differences in LA bioavailability per se.

To address these important issues, a pilot study was performed to establish the form of LA that is most effectively absorbed in elder subjects and whether there are differences in pharmacokinetics between healthy young and old volunteers. Results herein show that a subset of these elder males demonstrate increased maximal plasma concentrations ($C_{\text{max}}$) decreased time to reach maximal concentration ($T_{\text{max}}$), and exhibited higher total plasma LA area under the curve (AUC) values over the 3 h time course following oral R-LA intake.
Conversely, young males tended to exhibit decreased $T_{\text{max}}$, increased $C_{\text{max}}$, and higher AUC following R,S-LA intake. Our results indicate that for the subjects in this study, relative bioavailability of R- and R,S-LA is dependent on age, with some additional influence of gender.

2. Materials and methods

2.1. Subjects

Nine elder (>75 years) subjects were recruited using the OSU Center for Healthy Aging LIFE registry. An additional 10 young adults (ages 18–45) were recruited through local advertisement. Subjects with conditions that would limit LA absorption (e.g. Crohn’s disease) and/or diseases (e.g. diabetes mellitus, diagnosed Metabolic Syndrome) that may interfere with endpoint measurements were excluded from the study. Additionally, smokers were excluded from this study, as were individuals who consumed significant amounts of nutritional supplements that contain LA. Volunteers were requested to stop taking any supplement containing LA for two weeks prior to the first blood collection.

2.2. Supplementation and plasma collection

All subjects were asked to fast for 12 h prior to blood collection. Water and a normal schedule of other medications were permitted. A saline-lock blood collection device was inserted in a vein of the antecubital fossa and 10 mL of blood was collected at baseline. The blood was heparinized, centrifuged immediately, and red blood cells separated from the plasma within 5 min or less following collection. Blood was discarded if hemolysis was detected and additional blood drawn. Subjects were given a colored, coated tablet containing 500 mg of either R- or R,S-LA (Mak Wood Inc, Grafton, WI) with water (200 mL) after the baseline sample was collected. Blood was collected over 3 h after supplementation, with collections every 5 min for the first hour, then every 30 min thereafter for the next 2 h. Three to ten days following initial LA ingestion and blood sampling, the same subjects returned and the supplementation and blood collection protocol were repeated until both LA isoforms under study are administered and analyzed. Each person acted as his/her own control. These procedures were approved by the Institutional Review Board (approval #3755) at Oregon State University and all subjects provided written informed consent.

2.3. Plasma preparation and derivatization

Plasma was prepared and derivatized similar to previous published reports [23–25] with modifications. For LA determination, isolated plasma was mixed with trifluoroacetic acid (TFA, 1.8%, vol/vol final) and dimethylformamide (18%, vol/vol final). LA was extracted from the sample by the addition of an equal volume of ethylacetate and centrifugation for 30 s at 12,000 × g. The organic phase was removed and saved in a separate vial. The extraction was repeated two more times and all organic phases combined. The organic phase was dried in a speed vacuum and resuspended in a solution of 20 mM tris(2-carboxyethyl)phosphine (TCEP), 5 mM 4-Fluoro-7-aminosulfonylbenzofurazan (ABD-F), and 100 mM sodium tetraborate, pH 10. This solution was allowed to react at room temperature for 10 min and filtered through a 0.2 um filter into HPLC vials. Standards were prepared from R- and R,S-LA diluted in a solution of 10% (vol/vol) N,N-dimethylformamide (DMF) and 1 mM
ethylenediaminetetraacetic acid (EDTA) then derivatized with ABD-F as above. The protocol was designed to determine authentic LA only, the reduced form of LA and metabolites were not monitored.

For glutathione (GSH) analysis, plasma was immediately mixed with an equal volume of 15% perchloric acid containing 10 mM diethylenetriamine pentaacetic acid. Samples were derivatized with dansyl chloride as described [26,27].

2.4. HPLC

LA derivatives were separated by HPLC using a LC-18 Supelcosil column (25 cm × 4.6 mm, 5 μm, Phenomenex, Torrance, CA). A linear gradient was generated starting with 98% Buffer A (95% water and 5% acetonitrile containing 0.1% TFA) and going to 98% Buffer B (5% water and 95% acetonitrile containing 0.1% TFA) over 40 min. There was a 1 min re-equilibration to initial conditions and 5 min recovery period between sample injections. The elution rate was set at 1 mL/min. ABD-F derivatives were detected with excitation at 380 nm and emission at 510 nm and were quantified relative to standards. All samples were analyzed individually without pooling.

GSH HPLC was run as described [26,27]. Derivatives were separated using a 3-aminopropyl Luna column (5 μm, 2 mm × 150 mm, Phenomenex, Torrance, CA) and dansyl chloride derivatized GSH was detected using fluorescence detection with 335 nm excitation and 515 nm emission (Table 1).

2.5. Data analysis

Data was graphed using Graphpad Prism software. \( C_{\text{max}} \) and \( T_{\text{max}} \) were determined directly from individual plasma concentration profiles. AUC was determined using the trapezoidal method. Elimination rates, volume distributions, clearance rates, and mean residence times were determined using noncompartmental analysis with WinNonlin 5.3 software (Pharsight Corp., Cary, NC).

3. Results

The current study was designed to evaluate the plasma bioavailability of both the R- and R,S-forms of LA that are currently commercially available. LA was detected in the plasma of human subjects following oral supplementation of a single LA dose. The use of an indwelling catheter allowed repeated blood draws from each subject while minimizing discomfort and stress. There were no reports of adverse reactions resulting from consumption of the supplements or from the sample collections. Also, none of the subjects left the study prior to its completion. To determine whether oral LA potentially affected plasma thiol redox status, GSH was monitored over the 3 h time course. Results showed that neither R- nor R,S-LA ingestion altered plasma GSH levels in either young or old subjects (data not shown). Between subjects, the range of plasma GSH was 0.31–12.9 μM, which is within the typical range for humans [28]. Since oral supplementation of LA does not acutely affect plasma thiol redox status, or acutely induce a systemic redox stress, at the concentration given, we conclude that it is safe to proceed with analyzing LA bioavailability in both age groups.
Because this was a pilot study, the data reported herein are presented as case studies from a sampling of the population divided into older adults and younger adults, as well as male and female. Due to the small sample size, statistical analysis was not performed on these results to avoid type II errors in hypothesis testing [29]. These results will be instrumental in power calculations for future clinical studies examining LA effects in various age and gender groups. The study utilized a crossover design so each subject received both supplements (Fig. 1A). The derivatization procedure enables analysis of both LA and dihydro-LA (the reduced form), though only authentic LA was detected and quantified. Moreover, as no chiral column was used, it was not possible to separate R,S-LA into the proportions of R- and S-LA that appeared in the plasma. Shown is a typical chromatogram profile of a subject’s plasma LA profile relative to authentic LA (Fig. 1B and C). Plasma values based on HPLC separation and quantification are provided for every subject on each form of the supplement (Fig. 2).

3.1. $C_{\text{max}}$

Oral LA supplementation resulted in its rapid appearance in plasma, with almost complete disappearance from the plasma by 3 h. The average $C_{\text{max}}$ for the elder males taking R-LA was 3706 ng/mL and was markedly higher than the $C_{\text{max}}$ for R,S-LA (2537 ng/mL) in this age group. Additionally, the average $C_{\text{max}}$ value following R-LA supplementation was substantially elevated in the elder population (3248.61 ng/mL) versus young subjects (1513.35 ng/mL) (Table 2). Inspection of individual $C_{\text{max}}$ values showed that two of the six older male subjects had peak plasma LA concentrations that were markedly higher than that found in the other members of the cohort, which largely accounted for the higher apparent average $C_{\text{max}}$ for R-LA versus R,S-LA in this group (Fig. 3A). With the exception of those two males, variability between subject groups is not substantially different. The majority of subjects in the remaining groups demonstrated higher $C_{\text{max}}$ values of LA following supplementation with the racemic mixture. Interestingly, within-subject variability, evaluated by the ratio of R,S-LA relative to R-LA, indicates that the young males have the greatest amount of variability in $C_{\text{max}}$ values between the two forms of LA tested (Fig. 3E). Conventional measures suggest that the ratio of two tested compounds should fall within 0.8–1.25 to be considered bioequivalent [30]. With this specification, the two forms of LA do not demonstrate equivalent $C_{\text{max}}$ values in the elder males or in the young males in this study (Table 3).

3.2. $T_{\text{max}}$

For the older adult group, it took an average of 21.94 min to reach maximal plasma concentration of R-LA, while it took substantially longer for the young subjects to reach peak levels in the plasma. With the exception of the young males, all groups averaged a shorter time to reach maximal concentration after taking R-LA compared to R,S-LA (Table 2). One man in the older group demonstrated a substantially extended time to reach $T_{\text{max}}$ after taking R,S-LA (90 min compared to the elder male group average of 40 min); otherwise, the aged subjects tended to display less within-subject variability in $T_{\text{max}}$ between the two forms of LA (Fig. 3B) than the other groups. Conversely, for young males taking R-LA, it took substantially longer to reach maximal plasma concentration (42 min) compared
to R-LA of all other groups (Table 2). The ratio of the $T_{\text{max}}$ values suggests that R- and R,S-LA are not equivalent in elder males, young males, or young females (Table 3).

3.3. Elimination
Within-subject variability for older males was noticeably elevated when the elimination rate, defined as the time to eliminate half of the maximal plasma LA concentration ($t_{1/2}$), was calculated. Half the subjects in that age-group demonstrated higher $t_{1/2}$ values while taking R-LA and only one subject showed a higher $t_{1/2}$ value while taking R,S-LA. Additionally, half of all elder subjects had increased $t_{1/2}$ values compared to the young subjects. Young subjects did not demonstrate marked differences in elimination rates between the two forms of LA (Fig. 3C and G).

3.4. AUC
The overall amount of LA in the bloodstream, AUC, for R-LA was greater for the older group (2026 ng h/mL) compared to the young group (1070 ng h/mL) (Table 2). This difference is a reflection of the greater $C_{\text{max}}$ values achieved in older subjects after taking R-LA (Fig. 3A). There were no noticeable differences between the age groups following R,S-LA supplementation. Within-subject variability for the area under the curves was not remarkably different between the age groups (Fig. 3H). The ratios of R- to R,S-LA indicate that the AUC of the two forms are not equivalent in young males (Table 3). The age-associated differences in bioavailability are also reflected in the mean residence time (MRT) of LA molecules. The elder group tended to present greater between subject variability in MRT, compared to young subjects (Fig. 3E).

4. Discussion
As LA is often supplemented in diabetic patients, as well as frequently taken by senior adults, it is important to understand the pharmacokinetics of this compound. It is also important to investigate the absorption profile of the natural R-form of LA as compared to the more commercially available racemic mixture. While there have been reports examining the bioavailability of LA in young subjects, and in subjects with various medical conditions, no studies have compared the plasma absorption characteristics of LA in the older adults to those in young subjects. It should be noted that the dose of LA used in this study is safe for human supplementation, as both forms of LA were well tolerated by all individuals with no medical complaints. Additionally, in agreement with in vitro experiments [31], we were able to verify that this rapid influx of LA does not adversely decrease the levels of GSH, a monothiol antioxidant, in the plasma. As a corollary, while cellular and animal model experiments have demonstrated that LA increases GSH levels over longer periods of supplementation [32–35], LA does not appreciably increase plasma GSH levels during a 3 h time course in humans. Thus, it is reasonable to suggest that plasma LA does not acutely alter plasma thiol redox status and does not acutely induce a systemic stress.

LA is taken up into cellular tissues by the sodium-dependent multivitamin transporter [36]. This protein is expressed in many tissues throughout the body including the liver, heart, kidneys, and the blood-brain barrier [36,37]. Our findings indicate that LA is rapidly cleared
from the blood, representing distribution to the tissues and rapid first-pass liver metabolism. Our results for younger volunteers are in agreement with previous findings regarding the rate of metabolism and clearance in young healthy subjects [3].

Interestingly, comparisons of male and female values revealed few noticeable differences. However, age markedly affects bioavailability characteristics of LA. The average R-LA $C_{\text{max}}$ for the older group was considerably higher than for younger adults, and the $C_{\text{max}}$ value we report for the younger group is similar to previous reports [38]. While older adults often have a reduced absorbance of small molecule vitamin and micronutrients, many of the subjects in the higher age group had enhanced bioavailability of both forms of LA, compared to the younger adults. The increased AUC observed in the subset of elder males could be due to a reduction in hepatic perfusion often seen in the older adults or reduced metabolism [39]. The R,S-LA $T_{\text{max}}$ values for young subjects determine in this study are similar to previous reports for young healthy subjects [3]. Interestingly, we found the older individuals generally reached R,S-LA $C_{\text{max}}$ values faster than the younger subjects, and the $T_{\text{max}}$ value for R-LA was even further reduced in the elder group. A recent report demonstrates that a novel formulation of LA results in increased bioavailability in the subjects tested [40]. Interestingly, the increased AUC values they report are similar to the values we observed in the subset of older males that had considerably increased plasma levels of LA. Thus physiological and formulation factors need to be considered when designing a treatment regimen.

The widely varying ratios of R- to R,S-LA on the indices examined indicate that these compounds are not bioequivalent within the subjects of this study. A larger sample size will be needed to extrapolate the bioequivalence to the greater population. We can conclude that within this population of subjects R- and R,S-LA are not processed the same way, or are not equally bioavailable, in each person. Additionally, the evident variability in these parameters increases with age. Considering that LA shows promise as an age-essential micronutrient, the variability in bioavailability needs to be considered and further studied in relation to the elder population in order to define the most optimal benefit from supplements.

Due to the fast rate of metabolism and the large number of detectable LA metabolites [41], it is possible that a metabolite may mediate the therapeutic effects of LA. We were unable to measure LA metabolites in the present study because of the lack of commercially available standards for quantification purposes, but future studies examining the pharmacokinetics of any active metabolite could prove insightful.

The pharmacokinetics of R- versus S-LA have been evaluated following supplementation with the racemic mixture in young males. While the $C_{\text{max}}$ was about twice as high for R-LA as for S-LA [4], it is important to note that no therapeutic indices have been evaluated to compare the natural form of LA to the racemic mixture. Further studies will be necessary to judge the equivalent value of these two compounds.

This study importantly reveals that the plasma level of LA in elderly subjects is as least as high as in young subjects, if not greater. Thus these subjects may have increased levels of LA available to distribute to tissues to generate greater beneficial effects. This is
pharmacologically relevant for cases of diabetes where LA can improve polyneuropathies [42], vascular dysfunction [43], and oxidative stress [44]. This is also relevant to the elder population that often has increased incidence of oxidative stress and cardiovascular dysfunction [45].

Acknowledgments

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Abbreviations

- LA: lipoic acid
- AUC: area under the curve
- $C_{\text{max}}$: maximal plasma concentration
- $T_{\text{max}}$: time to reach $C_{\text{max}}$
- GSH: glutathione
- TCEP: tris(2-carboxyethyl)phosphine
- ABD-F: 4-Fluoro-7-aminosulfonylbenzofurazan
- EDTA: ethylenediaminetetraacetic acid
- TFA: trifluoroacetic acid
- $t_{1/2}$: time to clear 1/2 of the maximal concentration
- MRT: mean residence time
- DNTB: 1-fluoro-2,4-dinitrobenzen
- DMF: N,N-dimethylformamide

References


Fig. 1. Study design and HPLC separation and detection of plasma lipoic acid
Subjects received either R-LA or R,S-LA in a cross-over design (A). An indwelling catheter was placed in subject’s arm to allow blood sampling. Subjects received a 500 mg oral supplement of either R- or R,S-LA. Blood samples were collected over a 3 h time course following supplementation (A). Plasma samples were derivatized to ABD-F, separated by HPLC, and LA was monitored by fluorescence detection and quantified to standards. Shown is a typical HPLC chromatogram for an authentic R-LA standard (B). A typical chromatogram of LA detection in the plasma is shown for a subject in the study (C).
Fig. 2. Plasma LA profiles for subject groups
The line traces present each individual’s detected LA concentrations during the study.
Fig. 3. **Individual pharmacokinetic parameters**

$C_{\text{max}}$ (A and F), $t_{\text{max}}$ (B and G), $t_{1/2}$ (C and H), AUC (D and I), and MRT (E and J) are presented in the panels. The pharmacokinetic values for R- and R,S-LA from each individual subject are connected with a line in graphs A–E. Within subject variability (F–J) is presented for each pharmacokinetic parameter as a ratio of R,S-LA relative to R-LA. Points landing above the horizontal axis indicate that a greater value was observed after the subject took R,S-LA, while points landing below the horizontal axis indicate that a greater value was observed after the subject took R-LA. The horizontal line indicates no difference between the two forms.
Table 1

Participant demographics.

<table>
<thead>
<tr>
<th></th>
<th>Elder males</th>
<th>Elder females</th>
<th>Young males</th>
<th>Young females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>79 ± 5</td>
<td>79 ± 3</td>
<td>31 ± 7</td>
<td>30 ± 8</td>
</tr>
<tr>
<td>Height (inches)</td>
<td>70 ± 2</td>
<td>61 ± 3</td>
<td>72 ± 3</td>
<td>67 ± 2</td>
</tr>
<tr>
<td>Weight (pounds)</td>
<td>192 ± 55</td>
<td>142 ± 12</td>
<td>197 ± 50</td>
<td>151 ± 20</td>
</tr>
<tr>
<td>Blood pressure (group average)</td>
<td>116/68</td>
<td>138/86</td>
<td>134/75</td>
<td>113/70</td>
</tr>
<tr>
<td>Number of participants</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>5</td>
</tr>
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</table>

Values are mean ± SEM.
Table 2  

Pharmacokinetic values.

<table>
<thead>
<tr>
<th></th>
<th>All elder</th>
<th>All young</th>
<th>Elder males</th>
<th>Elder females</th>
<th>Young males</th>
<th>Young females</th>
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<tbody>
<tr>
<td>R-LA C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>3248 ± 809</td>
<td>1513 ± 341</td>
<td>3706 ± 1157</td>
<td>2318 ± 728</td>
<td>1157 ± 452</td>
<td>1862 ± 447</td>
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<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (min)</td>
<td>21.9 ± 2</td>
<td>36.1 ± 5</td>
<td>23 ± 3</td>
<td>20 ± 3</td>
<td>42 ± 8</td>
<td>26 ± 4</td>
</tr>
<tr>
<td>AUC (ng h/mL)</td>
<td>2026 ± 404</td>
<td>1070 ± 166</td>
<td>2388 ± 547</td>
<td>1792 ± 648</td>
<td>1070 ± 235</td>
<td>1601 ± 181</td>
</tr>
<tr>
<td>λ&lt;sub&gt;z&lt;/sub&gt; (h&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.760 ± 0.15</td>
<td>1.035 ± 0.13</td>
<td>0.752 ± 0.24</td>
<td>0.903 ± 0.27</td>
<td>1.05 ± 0.25</td>
<td>1.02 ± 0.20</td>
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<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (min)</td>
<td>70 ± 11</td>
<td>39 ± 2</td>
<td>80 ± 14</td>
<td>49 ± 14</td>
<td>40 ± 3</td>
<td>38 ± 3</td>
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<tr>
<td>MRT (h)</td>
<td>1.25 ± 0.2</td>
<td>1.02 ± 0.2</td>
<td>1.28 ± 0.3</td>
<td>1.35 ± 0.4</td>
<td>0.91 ± 0.2</td>
<td>1.07 ± 0.3</td>
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<table>
<thead>
<tr>
<th></th>
<th>All elder</th>
<th>All young</th>
<th>Elder males</th>
<th>Elder females</th>
<th>Young males</th>
<th>Young females</th>
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<tr>
<td>R,S-LA C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>2550 ± 423</td>
<td>2480 ± 261</td>
<td>2537 ± 508</td>
<td>2578 ± 930</td>
<td>2732 ± 411</td>
<td>1983 ± 319</td>
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<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (min)</td>
<td>35.3 ± 7</td>
<td>42.5 ± 8</td>
<td>40 ± 12</td>
<td>27 ± 4</td>
<td>37 ± 11</td>
<td>51 ± 11</td>
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<tr>
<td>AUC (ng h/mL)</td>
<td>1899 ± 236</td>
<td>1772 ± 143</td>
<td>1998 ± 271</td>
<td>1842 ± 591</td>
<td>1694 ± 229</td>
<td>1727 ± 217</td>
</tr>
<tr>
<td>λ&lt;sub&gt;z&lt;/sub&gt; (h&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.977 ± 0.19</td>
<td>0.797 ± 0.14</td>
<td>0.879 ± 0.26</td>
<td>1.171 ± 0.33</td>
<td>0.689 ± 0.22</td>
<td>0.905 ± 0.27</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (min)</td>
<td>67 ± 17</td>
<td>47 ± 2</td>
<td>70 ± 24</td>
<td>49 ± 24</td>
<td>49 ± 2</td>
<td>46 ± 4</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>1.29 ± 0.2</td>
<td>1.18 ± 0.2</td>
<td>1.40 ± 0.3</td>
<td>1.05 ± 0.4</td>
<td>1.56 ± 0.2</td>
<td>1.05 ± 0.26</td>
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</table>

The average values ± SEM are presented for each group (λ<sub>z</sub> = elimination rate constant).
## Table 3

Ratio of R-LA/R-S-LA for each pharmacokinetic measure.

<table>
<thead>
<tr>
<th>R/S ratio</th>
<th>All elder</th>
<th>All young</th>
<th>Elder males</th>
<th>Elder females</th>
<th>Young males</th>
<th>Young females</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>1.26*</td>
<td>0.79*</td>
<td>1.4*</td>
<td>0.97</td>
<td>0.43*</td>
<td>1.16</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>0.76*</td>
<td>0.97</td>
<td>0.74*</td>
<td>0.81</td>
<td>1.35*</td>
<td>0.59*</td>
</tr>
<tr>
<td>AUC</td>
<td>1.03</td>
<td>0.85</td>
<td>1.08</td>
<td>0.94</td>
<td>0.65*</td>
<td>1.01</td>
</tr>
<tr>
<td>$\lambda_z$</td>
<td>0.78*</td>
<td>1.30*</td>
<td>0.86</td>
<td>0.77*</td>
<td>1.52*</td>
<td>1.13</td>
</tr>
<tr>
<td>$t_{1/2}$</td>
<td>1.29*</td>
<td>0.77*</td>
<td>1.17</td>
<td>1.30*</td>
<td>0.66*</td>
<td>0.91</td>
</tr>
<tr>
<td>MRT</td>
<td>1.17</td>
<td>0.86</td>
<td>0.91</td>
<td>1.76*</td>
<td>0.59*</td>
<td>1.02</td>
</tr>
</tbody>
</table>

Values outside of the bioequivalence range of 0.8–1.25 are indicated with an asterisk (*). $\lambda_z$ = elimination rate constant.