Frank Bittner, DO
Charles Murchison, MS
Dennis Koop, PhD
Dennis Bourdette, MD
Rebecca Spain,
MD, MSPH

*Neurol Neuroimmunol
Neuroinflamm*
2017;4:e380; doi: 10.1212/
NXL.0000000000000380

LIPIC ACID PHARMACOKINETICS AT BASELINE AND 1 YEAR IN SECONDARY PROGRESSIVE MS

OPEN

Lipoic acid (LA) is a water- and fat-soluble oral anti-oxidant with anti-inflammatory properties. It has demonstrated benefits in animal models of MS and has been evaluated for MS relapse prevention and neuroprotection. However, there are relatively few data regarding LA pharmacokinetics (PK) in elderly populations or with use beyond 4 days.¹ In addition, studies have used a variety of doses, a wide age range of subjects, and have measured, at times, specific enantiomers rather than the more commercially available racemic form.²

Methods. Presented herein are PK results drawn at baseline and 1 year in the LA cohort of patients with secondary progressive MS enrolled in a randomized placebo-controlled trial of daily oral LA. The study was approved by the Veterans Affairs Portland Health Care System and Oregon Health & Science University Institutional Review Boards. Patients arrived after fasting for the prior 10 hours, and a predose sample was taken. Patients ate a meal immediately followed by 1,200 mg racemic LA (Pure Encapsulations, Sudbury, MA). Blood draws occurred at 30, 60, 90, 120, and 240 minutes after dose. Blood was allowed to clot at room temperature; serum was separated by centrifugation and stored at -80°C until batch analysis by mass spectrometry.³

Noncompartmental analysis determined pertinent PK parameters, including peak concentration (C_{max}), time at peak concentration (T_{max}), and observed bioavailability based on area under the curve (AUC) using common pharmacodynamics calculations. Baseline and 1-year differences were assessed using mixed models to account for serial correlation in the repeated measures and accommodate subjects with missing data at 1 year.

Results. Fifty-four patients were randomized in the parent trial, and of the 28 assigned to LA, 27 took at least 1 dose of LA and were included in PK analysis. Patients demonstrated 87% compliance by pill counts. The average age of the LA cohort was 57.9 (SD 6.7) years, 59% were women, and 96% were Caucasian. The average disease duration was 30.9

(SD 9.3) years, and the median Expanded Disability Status Scale score was 5.5 (range 3.0–8.0). The mean baseline C_{max} was 14.9 ± 11.9 nmol/mL with a non-significant reduction at 1 year (11.3 ± 7.3 , $p = 0.17$, figure, A). At baseline, the largest proportion of subjects (13, 48%) had C_{max} values at the 90-minute draw, whereas at year 1, the largest plurality (9, 41%) had a C_{max} value at the 120-minute draw, although this shift was not significant ($p = 0.47$). There was a nonsignificant reduction in bioavailability at 1 year (AUC 1407 ± 873 nmol/mL vs 1116 ± 647 nmol/mL, $p = 0.10$). Variability as measured by coefficient of variation (CV) was similar at baseline and 1 year (79.8% vs 64.9%), indicating stability in the PK measures, although the within-subject C_{max} values at 30 minutes were often discrepant between years (158.5% and 179.4%, figure, B). The patients (103, 114, 144, 147, and 155) terminating early (glomerulonephritis, MRI intolerance, prostate cancer, gastrointestinal [GI] intolerance, and renal failure, respectively) did not have observably high C_{max} levels.

Discussion. Overall, patients maintained peak serum levels of daily oral LA, although there were nonsignificant reductions toward lower and later absorptions at 1 year. C_{max} values occurred later (between 90 and 120 minutes) than a previous PK study of LA using the same dosing regimen (between 60 and 90 minutes).³ Because of limited clearance data, the analysis was unable to calculate many common, tail-based noncompartmental analysis parameters, including half-life. Although the mean C_{max} values were similar between baseline and 1 year, visual observation demonstrates high between-subject variability for the same year and within-subject variability between years based on the high coefficients of variation ($\text{CV} > 65\%$). A review of apparent outliers (115, 134, 137, and 149) did not reveal underlying differences (e.g., age, weight, and concomitant medications), nor were their mean brain atrophy rates different from the larger cohort. Breithaupt-Grögler et al. (1999) also noted high between-individual variability in C_{max} values of LA (99% and 96% of the measured R and S LA enantiomers at the highest dose of 600 mg of racemic LA). Reasons for between- and within-subject

(A) LA concentration at 6 time points over 120 minutes at baseline ($n = 27$) and 1 year ($n = 22$). Shown are mean values with SD bars. (B) Individual traces of baseline and 1-year mean LA peak concentrations. Variability measured by the mean coefficient of variation across the pharmacokinetic trace was similar at the 2 time points (79.8% vs 64.9%, respectively) with the highest variability found at 30 minutes (158.5% and 179.4%, respectively). LA = lipoic acid.

variable absorptions may be due to an elderly population with erratic GI absorption, reduced hepatic perfusion, or drug-drug interactions. Alternatively,

it may relate to intrinsic properties of LA or its delivery system.^{4–6} Yet unknown is if the PK variability and rapid clearance of LA impacts its

therapeutic efficacy or has dosing implications for clinical trials or clinical use. Further development of LA may depend on improving its bioavailability and tolerability. These PK data represent the longest duration use of LA in an MS-specific population.

From the VA Portland Health Care System (F.B., C.M., D.B., R.S.), OR; and Oregon Health & Science University (F.B., C.M., D.K., D.B., R.S.), Portland.

Author contributions: Frank Bittner: manuscript writing. Charles Murchison: statistical analysis and manuscript editing. Dennis Koop: data collection and manuscript editing. Dennis Bourdette: data interpretation. Rebecca Spain: data collection, data interpretation, and manuscript editing.

Acknowledgment: Pure Encapsulations, Sudbury, MA, provided the lipoic acid and placebo.

Study funding: Department of Veterans Affairs (B7493-W, R. Spain), National Institutes of Health (UL1TR000128).

Disclosure: F. Bittner received travel funding from the National Multiple Sclerosis Society. C. Murchison received research support from NINDS. D. Koop served on the editorial board for Drug Metabolism and Disposition. D. Bourdette received travel funding from the National Multiple Sclerosis Society, Consortium of MS Centers, and Paralyzed Veterans of America; is on the editorial board for Neurology; holds a patent for the treatment of multiple sclerosis with cyclic peptide derivatives of cyclosporin; has a patent pending for thyromimetic drugs for stimulating remyelination in multiple sclerosis; consulted for Magellan Health, Best Doctors, inc; and received research support from the National MS Center. R. Spain received research support from Biogen, Department of Veterans Affairs, Oregon Clinical and Translational Research Institute, VA Portland Health Care System, Oregon Health & Science University, and National MS Society, Conrad Hilton Foundation, Medical Research Foundation of Oregon, Race to Erase MS. Go to Neurology.org/nn for full disclosure forms. The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Received March 10, 2017. Accepted in final form May 21, 2017.

Correspondence to Dr. Bittner: Bittnerf@ohsu.edu

1. Teichert J, Hermann R, Ruus P, Preiss R. Plasma kinetics, metabolism, and urinary excretion of alpha-lipoic acid following oral administration in healthy volunteers. *J Clin Pharmacol* 2003;43:1257–1267.
2. Hermann R, Mungo J, Cnota P, Ziegler D. Enantiomer-selective pharmacokinetics, oral bioavailability, and sex effects of various alpha-lipoic acid dosage forms. *Clin Pharmacol* 2014;6:195–204.
3. Yadav V, Marracci G, Munar M, et al. Pharmacokinetic study of lipoic acid in multiple sclerosis: comparing mice and human pharmacokinetic parameters. *Mult Scler* 2010;16:387–397.
4. Breithaupt-Grögler K, Niebch G, Schneider E, et al. Dose-proportionality of oral thioctic acid—coincidence of assessments via pooled plasma and individual data. *Eur J Pharm Sci* 1999;8:57–65.
5. Klotz U. Pharmacokinetics and drug metabolism in the elderly. *Drug Metab Rev* 2009;41:67–76.
6. Phua L, New L, Goh C, Neo A, Browne E, Chan E. Investigation of the drug-drug interaction between alpha-lipoic acid and valproate via mitochondrial beta-oxidation. *Pharm Res* 2008;25:2639–2649.

Neurology® Neuroimmunology & Neuroinflammation

Lipoic acid pharmacokinetics at baseline and 1 year in secondary progressive MS

Frank Bittner, Charles Murchison, Dennis Koop, et al.

Neurol Neuroimmunol Neuroinflamm 2017;4;

DOI 10.1212/NXI.0000000000000380

This information is current as of June 28, 2017

Updated Information & Services	including high resolution figures, can be found at: http://nn.neurology.org/content/4/5/e380.full.html
References	This article cites 6 articles, 0 of which you can access for free at: http://nn.neurology.org/content/4/5/e380.full.html##ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Clinical trials http://nn.neurology.org/cgi/collection/all_clinical_trials Multiple sclerosis http://nn.neurology.org/cgi/collection/multiple_sclerosis
Permissions & Licensing	Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: http://nn.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://nn.neurology.org/misc/addir.xhtml#reprintsus

Neurol Neuroimmunol Neuroinflamm is an official journal of the American Academy of Neurology. Published since April 2014, it is an open-access, online-only, continuous publication journal. Copyright Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.. All rights reserved. Online ISSN: 2332-7812.