



Short Communication

Pharmacokinetics of oral L-serine supplementation in a single patient

Danny E. Miller^{a,b}, Carlos R. Ferreira^c, Anna I. Scott^{d,e}, Irene J. Chang^{b,*}^a Department of Medicine, Division of Medical Genetics, University of Washington, Seattle, Washington, USA^b Department of Pediatrics, Division of Genetic Medicine, University of Washington, Seattle, Washington and Seattle Children's Hospital, Seattle, Washington, USA^c National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA^d Department of Laboratories, Seattle Children's Hospital, Seattle, Washington, USA^e Department of Laboratory Medicine, University of Washington, Seattle, Washington, USA

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ABSTRACT

Serine, a non-essential amino acid, has attracted clinical attention because of potential benefit in certain metabolic and neurological disorders. Despite the therapeutic potential, little is known about the pharmacokinetics of L-serine metabolism in humans. Here we present pharmacokinetic data at the time of treatment initiation as well as plasma serine levels during dose escalation from a single individual taking oral L-serine as part of a treatment regimen. Our results show that plasma serine levels rise and fall rapidly after oral L-serine intake, suggesting that the optimal dosing for oral L-serine supplementation is at least three times per day.

1. Introduction

Next-generation sequencing has allowed for the association of previously unknown genes and pathways with complex human phenotypes. These associations suggest new treatment modalities for previously untreatable rare diseases. Examples are disorders which may benefit from amino acid supplementation.

For example, variants in the gene encoding serine palmitoyl-transferase (*SPTLC1*) have been shown to cause both macular telangiectasia type 2 and hereditary sensory and autonomic neuropathy type 1 (HSAN1) or each disorder separately [4]. Variants in *SPTLC1* are thought to result in abnormal incorporation of L-alanine or L-glycine instead of L-serine during sphinganine synthesis, which leads to the accumulation of neurotoxic byproducts, 1-deoxy-sphinganine, 1-deoxymethyl-sphinganine, and 1-deoxy-ceramides or other derivatives. Mouse models of HSAN1 suggested that increases in dietary serine could lead to decreased levels of these neurotoxic byproducts, with similar observations made in a pilot study of oral serine supplementation in individuals with HSAN1 [3,5]. Thus, there is therapeutic potential for serine supplementation in these rare diseases.

Unfortunately, data regarding the pharmacokinetics of L-serine are lacking; there is an unmet need for careful observations in individuals taking oral supplementation. Creating accurate models of serine metabolism is challenging as evidenced by the wide range of values that have been reported in the literature [2,6]. Part of these challenges arise from variability in the endogenous production of serine in the body [6].

Here, we report pharmacokinetic values for a female teenage patient with a variant in *SPTLC1* causing a neuromuscular phenotype initiating oral L-serine supplementation. We provide data for both a single dose, and values of plasma serine measured during a 3-month treatment and dose escalation period. This data may inform the design of future treatments and trials using L-serine as a supplement.

2. Materials and methods

2.1. Study approval

The patient was enrolled in study #1831 approved by the institutional review board of Seattle Children's Hospital.

2.2. Plasma serine measurements

L-serine in 500 mg tablets was obtained from Jo Mar Labs (Watsonville, CA). The patient stopped all multivitamins and oral supplements at least 1 week prior to initiation of treatment.

Data for this study is presented over two timepoints. First, pharmacokinetic data is presented for a three-hour sample period prior to the patient beginning regular serine supplementation (Fig. 1). Treatment was started with 227 mg/kg of serine divided three times per day, or 2 g of serine three times a day. Plasma amino acids were obtained prior to the first 2 g oral dose of serine, then 30, 60, 120, and 180 min after dosing. Amino acids were measured using routine clinical

* Corresponding author at: Departments of Pediatrics, Division of Genetic Medicine, Biochemical Genetics Program, 4800 Sand Point Way NE, MS/OC.6.835, Seattle Children's Hospital, Seattle, WA 98105, USA.

E-mail address: ijchang@uw.edu (I.J. Chang).

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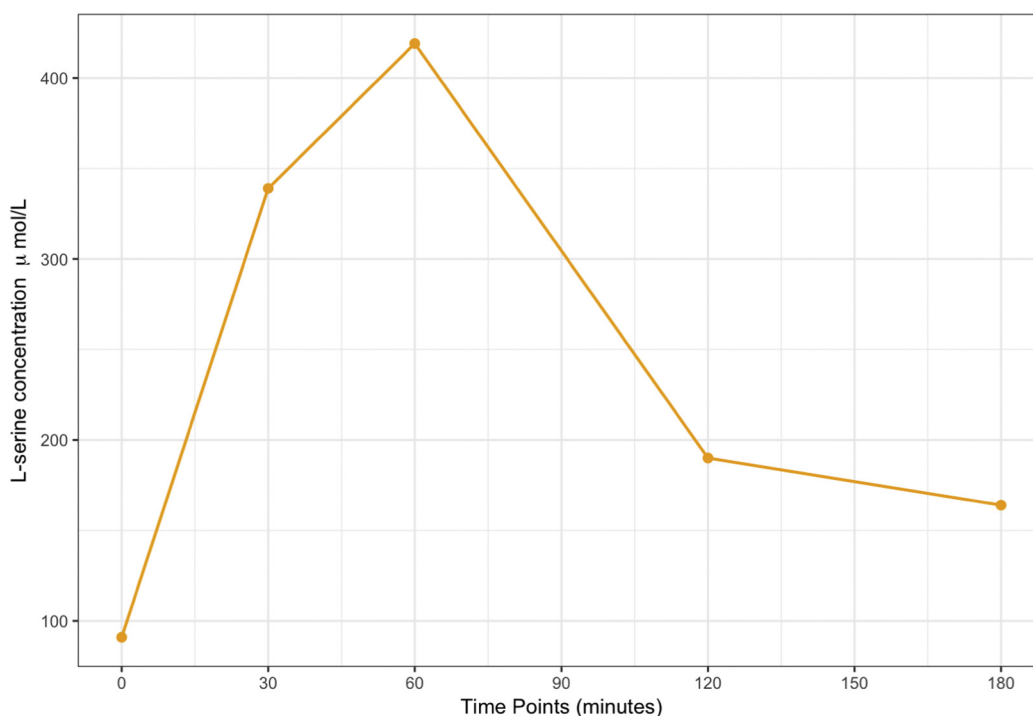


Fig. 1. Plasma L-serine concentration after one oral dose of L-serine (time 0 min). Data was collected prior to the patient beginning daily supplementation. The patient was fasting prior to and during the sampling.

laboratory methods for plasma amino acid quantification using a Biochrom 30+ instrument and ninhydrin detection (Biochrom Ltd., Cambridge, UK).

Second, plasma amino acids were measured at specific intervals prior to and during treatment (Supplementary Table 1). During this time, the dose of serine was increased slowly to a goal of 400 mg/kg during the second month of treatment.

2.3. Calculation of pharmacokinetic data

Non-compartmental analysis of pharmacokinetic parameters was performed using PK Solver 2.0 [8]. The terminal elimination rate constant was calculated using three observations in the terminal slope. The AUC calculation method was linear trapezoidal. For calculation of clearance and apparent volume of distribution after oral dosing, a bioavailability of 60% was used based on previously published extraction data [2,7].

3. Results

Plasma serine concentrations were measured from five blood samples collected over a three-hour period (Fig. 1). Time 0 is immediately prior to initiation of oral treatment. Pharmacokinetic calculations based on the serine concentrations are shown in Table 1.

Plasma serine levels were also measured during a 3-month dose escalation period. Dose was divided three times per day and increased slowly over time from 227 mg/kg to 400 mg/kg. While the timing of the oral dose of serine and blood draws was not controlled, we find that plasma serine levels remained elevated during the observation period. A single low serine value of 170 μmol/L may be due to the timing of supplementation relative to the blood draw (Supplementary Table 1).

4. Discussion

Here we report both pharmacokinetic and long-term plasma levels of a patient taking oral L-serine. Multiple samples obtained at treatment

Table 1

Pharmacokinetic data calculated from plasma serine measurements. Definitions: L, liters; h, hours; λ_z , terminal elimination rate constant which represents the rate of elimination only; AUC, area under the curve, a measure of systemic exposure of a drug to the body; AUMC, area under the first moment of the plasma concentration-time curve; MRT, the average time a molecule stays in the body; AUC, AUMC, and MRT are calculated for either time zero to 3 h after dose (t_0-t_3) or from time zero to infinity ($t_0-\infty$); CL, clearance, volume of plasma cleared of drug per hour; Vd, volume of distribution, amount of drug in the body divided by the plasma concentration; $t_{1/2}$, elimination half-life, time it takes for plasma concentration to fall by 50%.

Parameter	Value
λ_z	0.47/h
AUC t_0-t_3	778.5 μmol*h/L
AUC $t_0-\infty$	1128 μmol*h/L
AUMC t_0-t_3	1025 μmol*h ² /L
AUMC $t_0-\infty$	2819 μmol*h ² /L
MRT t_0-t_3	1.3 h
MRT $t_0-\infty$	2.5 h
CL	10.1 L/h
Vd	21.6 L
$t_{1/2}$	1.48 h

initiation revealed a rapid increase in plasma concentration of serine and corresponding rapid decline. This is consistent with data recently reported by Bosley and colleagues [2] who gave 10 study members 20 g of serine for 2 days and observed a similar rapid spike followed by decline in serine levels.

Dosing was based on a study of patients with HSAN1 taking oral L-serine supplementation at either a low dose of 200 mg/kg or 400 mg/kg [3,5]. Given the limited data on serine supplementation we began supplementation at 200 mg/kg then slowly increased to a target dose of 400 mg/kg (Supplementary Table 1). We find that serine levels

remained appropriately elevated during the observation period. Serum serine levels at both 200 mg/kg/day and 400 mg/kg/day were similar to those reported by Auranen and colleagues [1].

Our pharmacokinetic data revealed an elimination half-life of 1.48 h, similar to the value of 1.45 h reported by Bosley et al. [2]. After five half-lives, 97% of steady state is achieved, thus 7.4 h after dose administration only 3% of serine will remain in circulation. From a practical standpoint, this means that optimal oral serine supplementation should be divided in three daily doses.

It is important to keep in mind that the data presented here come from a patient with a genetic disorder that may benefit from serine supplementation. Data from patients with disorders which affect the normal use of serine in the body may give falsely elevated or depressed values. Overall, it is reassuring that our observed elimination half-life is similar to that recently reported for 10 healthy individuals [2].

As the number of rare disorders which may benefit from treatment by oral amino acid supplementation increases, the need for additional pharmacokinetic data will increase. Thus, measurements of both healthy individuals and those with a disorder which may benefit from serine supplementation will help to better define the true pharmacokinetics of L-serine metabolism in humans.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ymgmr.2020.100607>.

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Declaration of Competing Interest

None.

References

- [1] M. Auranen, J. Toppila, S. Suriyanarayanan, M.A. Lone, A. Paetau, et al., Clinical and metabolic consequences of L-serine supplementation in hereditary sensory and autonomic neuropathy type 1C, *Cold Spring Harb Mol. Case Stud.* 3 (2017) a002212, <https://doi.org/10.1101/mcs.a002212>.
- [2] J. Bosley, E. Bjornson, C. Zhang, H. Turkez, J. Nielsen, et al., Informing pharmacokinetic models with physiological data: oral population modeling of L-serine in humans, *Medrxiv* 2019 (2019), <https://doi.org/10.1101/2019.12.07.19011429>.
- [3] V. Fridman, S. Suriyanarayanan, P. Novak, W. David, E.A. Macklin, et al., Randomized trial of L-serine in patients with hereditary sensory and autonomic neuropathy type 1, *Neurology* 92 (2019) e359–e370, <https://doi.org/10.1212/wnl.0000000000006811>.
- [4] M.L. Gantner, K. Eade, M. Wallace, M.K. Handzlik, R. Fallon, et al., Serine and lipid metabolism in macular disease and peripheral neuropathy, *New Engl. J. Med.* (2019), <https://doi.org/10.1056/nejmoa1815111>.
- [5] K. Garofalo, A. Penno, B.P. Schmidt, H.-J. Lee, M.P. Frosch, et al., Oral L-serine supplementation reduces production of neurotoxic deoxysphingolipids in mice and humans with hereditary sensory autonomic neuropathy type 1, *J. Clin. Invest.* 121 (2011) 4735–4745, <https://doi.org/10.1172/jci57549>.
- [6] S.C. Kalhan, R.W. Hanson, Resurgence of serine: an often neglected but indispensable amino acid, *J. Biol. Chem.* 287 (2012) 19786–19791, <https://doi.org/10.1074/jbc.r112.357194>.
- [7] E.P.J.G. Neis, S. Sabrkhany, I. Hundscheid, D. Schellekens, K. Lenaerts, et al., Human splanchnic amino-acid metabolism, *Amino Acids* 49 (2016) 161–172, <https://doi.org/10.1007/s00726-016-2344-7>.
- [8] Y. Zhang, M. Huo, J. Zhou, S. Xie, PKSolver: an add-in program for pharmacokinetic and pharmacodynamic data analysis in microsoft excel, *Comput. Methods Prog. Biomed.* 99 (2010) 306–314, <https://doi.org/10.1016/j.cmpb.2010.01.007>.