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Research Article

The Pharmacokinetics of Orally Administered Calcium Pantothenate in Healthy Adults

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Abstract

Pantothenic acid, aka Vitamin B5, is essential for production of coenzyme-A, an important component of energy metabolism. The pharmacokinetics (PK) of orally administered calcium pantothenate are not well characterized. This single-center, open-label study of 40 adults investigated single and multidose PK of orally administered calcium pantothenate. Tolerability of high doses and impact of food were also evaluated. This study included Single Ascending Dose (SAD) and Multiple Dose (MD) periods. For the SAD, four sequential cohorts of 8 subjects received single doses of calcium pantothenate after an overnight fast. Doses were 500 mg, 1000 mg, 2000 mg and 5000 mg; with the 5000 mg dose repeated following a 2-week washout and after a high-fat meal. In the MD period, 8 subjects received 2000 mg daily for 14 days. PK samples were collected for 192 hours post-last dose in the SAD and MD periods, with frequent sampling on Days 1 and 14, and pre-dose samples on Days 12 and 13 in the MD group. Absorption was rapid with peak concentrations reached approximately 1-hour post-dose under fasted conditions. Exposure (AUC) increased with dose from 500 to 2000 mg with no further increase between 2000 and 5000 mg. Terminal half-life averaged 225 hours. Peak exposure (Cmax) increased greater than dose-proportionally from 500 to 2000 mg. Food delayed absorption by 2 hours (1.002 versus 2.995 hours), and increased AUC by 55%. Steady state was achieved by Day 14 with a 3.1-fold accumulation for AUC0-24. No deaths, serious adverse events, or discontinuations for adverse events occurred.

Keywords: Healthy adults, Pantothenic acid, Calcium pantothenate, Coenzyme-A, Pharmacokinetics, Vitamin B5

Abbreviations: AE: Adverse Event; ANOVA: Analysis of Variance; AUC: Area Under the Curve; BLQ: Below the Limit of Quantitation; BMI: Body Mass Index; cm: Centimeter; Cmax Maximum / Peak Concentration; CoA: Coenzyme-A; CPK: Creatine Phosphokinase; CV: Coefficient of Variation; DN: Dose Normalized; ECG: Electrocardiogram; FDA: Food and Drug Administration; GRAS: Generally Regarded As Safe; hr: Hour; Kg, Kilogram; Kg/m^2: Kilogram per Square Meter; LC-MS/MS: Liquid Chromatography-Tandem Mass Spectrometry; LLOQ: Lower Limit of Quantitation; LSM: Least-Squares Means; MCADD: Medium Chain Acyl-CoA Dehydrogenase Deficiency; MD: Multiple Dose; MedDRA®: Medical Dictionary for Regulatory Activities; mg: Milligram; mL, Milliliter; N, Sample Size; n: Number of Observations; ng: Nanogram; PK: Pharmacokinetic; PKAN: Pantothenate Kinase-Associated Neurodegeneration; RDA: Recommended Daily Allowance; SAD: Single Ascending Dose; SAE, Serious Adverse Event; SD: Standard Deviation; SEM: Standard Error of the Mean; USA: United States of America

Introduction

Pantothenic acid, also called Vitamin B5, is a water-soluble vitamin essential for the production of coenzyme-A (CoA). CoA forms a bond with acyl carbons and mediates acyl transfer reactions in over 70 enzymatic pathways and is estimated to be involved in

4% of all biochemical reactions [1,2]. As an important component of human energy metabolism, impairments in the CoA pathway are implicated in numerous hereditary and acquired conditions including pantothenate kinase-associated neurodegeneration (PKAN) and medium chain acyl-coA dehydrogenase deficiency (MCADD) [3-5].

Oral supplements consisting of 250 or 500 mg of calcium pantothenate are "generally regarded as safe" (GRAS) in humans and are widely available over the counter. The adequate intake level for adults in the USA is 5 mg/day, but currently there are insufficient data to determine a recommended daily allowance (RDA) [6]. Pantothenate appears to be quite safe in humans with studies describing the administration of doses of up to 10 grams per day over prolonged periods of time [7] and, accordingly, no upper limit for tolerability have been established. A pantothenic acid-based dietary supplement has been utilized successfully to treat adults with acne vulgaris and has been hypothesized as a potential treatment for patients with other issues of the CoA pathway [8,9]. However, understanding and optimizing pantothenate dosing is critical to the optimization of these therapeutic strategies.

Despite its wide availability, the PK of calcium pantothenate, especially at higher doses, has not been well described. The current study sought to determine the single dose PK of 500 to 5000 mg of orally administered calcium pantothenate in healthy subjects. Further, the effect of food on PK, steady-state PK, and the safety and tolerability of 14-days of high dose calcium pantothenate supplementation was investigated.

Materials and Methods

Ethics

The study was conducted in accordance with the ethical standards of the Institutional Review Board, the European Union directive 2001/20/EC, Good Laboratory Practice, and the ethical principles set forth in the Declaration of Helsinki of 1975 as revised in 1983. The study protocol was approved by the Advarra, Inc. Institutional Review Board. Signed informed consent was obtained from each subject prior to enrollment in the study and all subject data was identified only by a unique study identification number.

Study Design

This was a single-center, open-label, 2-part study of calcium pantothenate administered orally to healthy adults: Part 1 was a Single Ascending Dose (SAD) investigation including a food effect portion and Part 2 was a Multiple Dose (MD) investigation with both parts conducted in healthy subjects assessing the safety, tolerability, and PK of oral calcium pantothenate administration. Enrolled subjects were admitted to a clinical research unit on the day prior to dosing and remained there per the timing requirement of their cohort as detailed below. All calcium pantothenate administered was in the form of Pantothenic Acid 500 mg Tablets (as D-Calcium Pantothenate) (Distributed by Rugby Laboratories, Livonia, MI USA) and was administered after an overnight fast of at least 10 hours under supervision with approximately 240 mL of water and followed by an additional 4 hours fast.

Eligible subjects were healthy adults, ages 18 to 55, 50 to 110 kg, and free of drug, alcohol, and nicotine use. Forty male and female (of non-childbearing potential) subjects were enrolled, 32 subjects in the SAD and 8 subjects in the MD. The use of any prescription drug, over-the-counter drug, herbal medication, routine vitamins or minerals, nutritional supplement, or any investigational agent during the study was prohibited.

SAD Investigation

The SAD portion of the study included 4 sequential cohorts of 8 healthy adults who were enrolled and received single oral doses of calcium pantothenate as seen in (Table 1). Subjects remained in the clinical research unit from the day prior to dosing through the 72-hour blood draw and returned for additional blood draws at the times indicated through final blood draw and study termination at Day 9.

Cohort Dosing	Conditions
Single Ascending Dose (SAD)	
500 mg Calcium Pantothenate on Day 1	After overnight fast
1000 mg Calcium Pantothenate on Day 1	After overnight fast
2000 mg Calcium Pantothenate on Day 1	After overnight fast
5000 mg Calcium Pantothenate on Day 1	After overnight fast
5000 mg Calcium Pantothenate on Day 1	Following a high-fat meal
Multiple Dose (MD)	
2000 mg Calcium Pantothenate daily for 14-days	After overnight fast

Table 1: Dosing Cohorts.

Clinical and laboratory safety data were reviewed prior to escalating the dose for the next cohort. The following pantothenate dose level were studied: 500, 1000, 2000, and 5000 mg. To assess food effect, subjects received 5000 mg calcium pantothenate on 2 occasions separated by a 2 to 3 week washout. The first administration was after an overnight fast, and the second was administered 30 minutes after the start of a high-fat breakfast. The meal was designed per FDA guidance and derived approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. Specifically, each subject ate two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of

hash brown potatoes and eight ounces of whole milk [10].

MD Investigation

Eight healthy adults were enrolled and received a 14-day course of daily 2000 mg calcium pantothenate administered each morning after an overnight fast. The dose was selected based on the PK results obtained in the SAD as it was demonstrated to be well tolerated and the dose beyond which plasma AUC0-inf plateaued (less than a 20% increase from the previous dose). Subjects remained in the clinical research unit through the Day 2 dose of study drug and returned daily for administration of study drug thereafter. Subjects were readmitted to the unit on Day 13 where they remained through the 72-hour post-dose on Day 14 and returned as needed for blood draws thereafter.

Pharmacokinetic Sample Timing and Analytics

For the SAD portion, blood samples for the determination of plasma pantothenate were collected pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 144, and 192 hours post-dose. For the MD portion, blood samples were taken pre-dose on Day 1 and 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours post-dose, and pre-dose on Days 12 and 13. On the last day of dosing (Day 14), samples were collected pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (Day 15), 48 (Day 16), 72 (Day 17), 96 (Day 18), 144 (Day 20), and 192 (Day 22) hours post-dose.

Plasma concentrations of pantothenate were determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantitation (LLOQ) of 40 ng/mL. Sample analysis was performed at Quest Diagnostics Nichols Institute (Valencia, CA USA). A noncompartmental PK approach was used to analyze individual plasma pantothenate concentration-time data (using Phoenix® WinNonlin® Version 7.0). Because the analyzed compound (pantothenate) was of a different moiety from calcium pantothenate, the appropriate dose adjustment was made for the calculation of dose-dependent PK parameters (CL/F, Vz/F, dose-normalized (DN) AUCinf and DN Cmax) based on a dose of 550 mg as calcium salt to 500 mg of free base.

Safety

Safety was evaluated by physical examinations, vital signs, 12-lead ECGs, clinical laboratory tests, and AEs. Physical exams were performed at screening and study completion with abbreviated physical exams at check-in and Day 4 for SAD, and at check-in for MD. Vital signs were collected pre-dose and 4 hours post-dose on Day 1 and upon awakening on remaining days. ECGs were done at screening and pre-dose and 4 hours post-dose on Day 1. Clinical laboratory tests including serum chemistry, hematology, and urinalysis were performed at screening, check-in, Day 2, Day 9 for single dose (study termination, SAD), Day 15 for MD, and Day 22 (study termination, MD). In the 5000 mg food effect group laboratory tests were repeated under fasted and fed conditions.

Statistics

Summary statistics (N, arithmetic mean, SD, CV%, SEM, minimum, median, maximum, geometric mean, and geometric CV%) were calculated for plasma pantothenate PK parameters were generated using SAS® version 9.3 or higher.

Dose proportionality was evaluated using a power model. A statistical linear relationship between the ln-transformed pantothenate PK parameters AUC0-t, AUC0-inf, and Cmax and the ln-transformed dose was fitted by using a regression model with ln-transformed dose as a covariate. Dose proportionality could not be rejected if a statistical linear relationship was demonstrated and the 95% Confidence Interval (CI) for the slope included the value of 1 for dose-dependent parameters.

An analysis of variance (ANOVA) was performed on the ln-transformed AUC0-t, AUC0-inf, and Cmax for the 5000 mg fasted and fed group. The ANOVA model included treatment as the fixed effect, and subject as a random effect. The ANOVA included calculation of least-squares means (LSM) as well as the difference between treatment LSM. Ratios of geometric LSM were calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed AUC0-t, AUC0-inf, and Cmax. These ratios were expressed as a percentage relative to the reference treatment (fasted). Ninety percent (90%) CIs for the ratios were derived by exponentiation of the CIs obtained for the difference between regimen LSM resulting from the analyses on the ln-transformed AUC0-t, AUC0-inf, and Cmax. The CIs were expressed as a percentage relative to the fasting regimen.

A visual inspection of the plasma pantothenate trough concentrations on Days 12 through 14 was performed in order to assess achievement of steady state. No formal statistical analysis was performed. All reported AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 21.0. AEs were tabulated by System Organ Class and Preferred Term. Descriptive and summary statistics were reported for numeric clinical laboratory, vital sign, and ECG results by time point for single-dose and multiple-dose cohorts. A shift table describing out-of-normal range shifts was provided for analysis of clinical laboratory results.

Results

Thirty-two subjects completed the SAD portion of the study and 8 completed the MD. The demographics are included in (Table 2).

		SAD					MD
Trait		**500 mg N=8**	**1000 mg N=8**	**2000 mg N=8**	**5000 mg N=8**	**Total N=32**	**2000 mg N=8**
Sex	Female	3 (38%)	6 (75%)	4 (50%)	1 (13%)	14 (44%)	4 (50%)
	Male	5 (63%)	2 (25%)	4 (50%)	7 (88%)	18 (56%)	4 (50%)
Race	Black or African American	2 (25%)	1 (13%)	0 (0%)	2 (25%)	5 (16%)	1 (13%)
	White	6 (75%)	7 (88%)	8 (100%)	6 (75%)	27 (84%)	7 (88%)
Ethnicity	Hispanic or Latino	4 (50%)	6 (75%)	5 (63%)	5 (63%)	20 (63%)	3 (38%)
	Not Hispanic or Latino	4 (50%)	2 (25%)	3 (38%)	3 (38%)	12 (38%)	5 (63%)
Age (years)	Mean (SD)	39.5 (9.90)	41.0 (13.02)	43.6 (11.17)	33.8 (7.96)	39.5 (10.79)	39.9 (7.10)
Weight (kg)	Mean (SD)	80.43 (13.27)	72.24 (7.60)	86.36 (10.58)	78.51 (11.42)	79.38 (11.57)	78.76 (12.27)
Height (cm)	Mean	169.6 (9.33)	163.5 (7.98)	166.3 (10.00)	175.0 (10.25)	168.6 (9.97)	167.4 (10.51)
BMI (kg/m²)	Mean	27.86 (3.39)	27.25 (4.39)	31.35 (3.92)	25.66 (3.29)	28.03 (4.16)	28.34 (5.65)
BMI, Body Mass Index; MD, Multiple Dose; SAD, Single Ascending Dose; SD, Standard Deviation							

Table 2: Demo Graphics.

SAD Portion

Pre-dose pantothenate concentrations in 19 out of 32 subjects was < LLOQ of the assay (40 ng/mL). In the remaining subjects, pre-dose pantothenate values were 83.6 ± 98.7 ng/mL. Mean concentrations peaked by one-hour post-dose and then declined in a multiphasic fashion (Table 3 and Figure 1); a similar profile shape was maintained at all doses. Concentrations remained measurable until 192 hours post-dose for all subjects with the exception of 2 subjects following administration of the 500 mg dose and 1 subject following the 1000 mg dose, whose below the limit of quantitation (BLQ) concentrations occurred earlier. Terminal t1/2 was longer than anticipated and could only be determined in 18 of the subjects where it averaged 225 hours. Similarly, AUC0-inf could not be determined without excessive extrapolation in the majority of subjects and AUC0-t was used to evaluate dose-proportionality and food effect. Following single ascending doses, overall exposure increased up to 2000 mg albeit in a slightly less than dose-proportional manner for AUC0-t but greater than dose-proportional for Cmax (Table 4). There was no further increase in exposure between 2000 and 5000 mg. The formal analysis rejected dose proportionality for AUC0-t and Cmax, although this was largely driven by the inclusion of the 5000 mg dose in the analysis. Dose proportionality was established at doses up to 2000 mg.

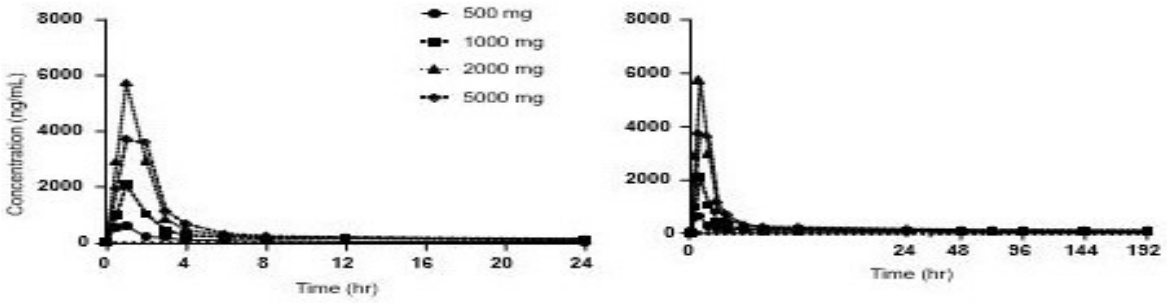

Figure 1: Mean Plasma Pantothenate Concentration Versus Time Profiles Following Administration of Single Ascending Oral Doses of Calcium Pantothenate Under Fasted Conditions (Linear Scale).

Pantothenate AUC0-t increased by 55% following the single 5000 mg dose under fed condition compared to fasted. Food also delayed absorption with a tmax of 3 hours vs. 1 hour fasting (Table 4 and Figure 2).

Pharmacokinetic Parameters	500 mg	1000 mg	2000 mg	5000 mg, fasted	5000 mg, fed
AUC_{0-t} (ng*hr/mL)	8953 (78.3) [n=8]	15010 (80.3) [n=8]	29120 (32.5) [n=8]	25630 (28.7) [n=8]	39670 (41.5) [n=8]
AUC_{0-inf}# (ng*hr/mL)	38820 (13.3) [n=3]	24860 [n=1]	52460 (50.9) [n=4]	49460 (26.5) [n=6]	64180 (25.5) [n=4]
$AUC_{\%extrap}$#	67.44 ± 0.80820 [n=3]	33.39 [n=1]	39.68 ± 13.821 [n=4]	44.55 ± 4.7810 [n=6]	41.25 ± 7.7021 [n=4]
C_{max} (ng/mL)	672.0 (48.7) [n=8]	1749 (94.8) [n=8]	5087 (72.8) [n=8]	3556 (93.0) [n=8]	4464 (111.6) [n=8]
T_{max} (hr)	1.000 (0.50, 2.00) [n=8]	1.000 (0.50, 1.00) [n=8]	1.035 (1.00, 2.06) [n=8]	1.002 (1.00, 2.01) [n=8]	2.995 (2.00, 4.01) [n=8]
$t_{1/2}$# (hr)	362.061 ± 19.5907 [n=3]	125.057 [n=1]	230.110 ± 180.4713 [n=4]	240.503 ± 50.8433 [n=6]	205.799 ± 43.3426 [n=4]
# - Extrapolated AUC is >25% in the majority of subjects. PK parameter is not robust and presented for information purposes only.					

Table 3: Plasma Pantothenate Pharmacokinetic Parameters in SAD.

Parameter	Geometric LSM, Fed	n	Geometric LSM, Fasted	n	GMR (%)	90% Confidence Interval (lower, upper)	Intra-subject CV%
AUC_{0-t} (ng*hr/mL)	39670	8	25630	8	154.83	134.23 - 178.59	15.16
AUC_{0-inf}# (ng*hr/mL)	64180	4	49460	6	129.77	79.90 - 210.75	26.16
C_{max} (ng/mL)	4464	8	3556	8	125.54	98.48 - 160.05	26.06
# - Extrapolated AUC is >25% in the majority of subjects. PK parameter is not robust and presented for information purposes only. Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA. Intra-subject CV% was calculated as 100 x square root (exp[MSE]-1), where MSE = Residual variance from ANOVA.							

Table 4: Statistical Analyses of Pantothenate Pharmacokinetic Parameters Following Administration of 5000mg Calcium Pantothenate Under Fasted and Fed Conditions.

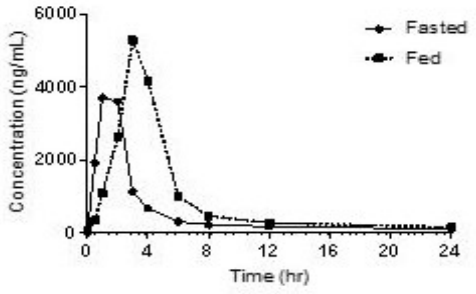

Figure 2: Mean Plasma Pantothenate Concentration Versus Time Profiles Following Administration of 5000 mg Calcium Pantothenate Under Fasted and Fed Conditions (Linear Scale).

MD Portion

Multiple 2000 mg oral doses for 14 consecutive days under fasted condition resulted in an accumulation in plasma pantothenate exposure over 24 hours (AUC0-24) by 3.1-fold (accumulation ratio RA,AUC; Accumulation ratio calculated from AUC0-24 at steady state and AUC0-24 following a single dose) and peak concentration by 2.5-fold. Based on visual inspection of the plasma pantothenate trough concentrations on Days 12 through 14, steady state was achieved by Day 14. The increase in trough plasma pantothenate concentrations between Day 12 and Day 13 was approximately 26% and the increase in concentration between Day 13 and Day 14 was approximately 5% (Table 5 and Figure 3).

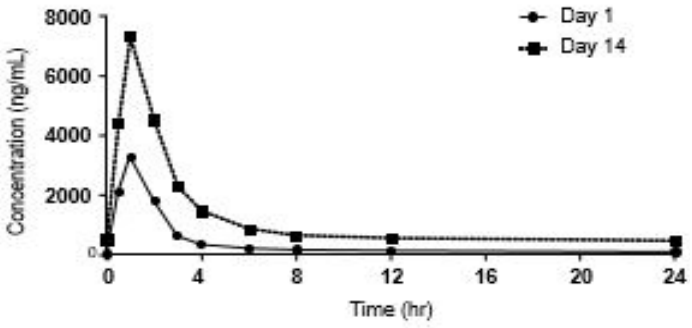

Figure 3: Mean Plasma Pantothenate Concentration Versus Time Profiles Following Administration of Multiple 2000 mg Oral Doses of 2000 mg Calcium Pantothenate for 14 Consecutive Days Under Fasted Conditions (Linear Scale).

Safety

No deaths, serious adverse events, or subject discontinuations due to adverse events occurred during this study (Table 6). Overall, 10 (31%) subjects experienced AEs in the SAD, and 3 (38%) of 8 subjects experienced AEs during the MD portion. There were no AEs reported during the 5000 mg fed portion of the study. AE incidence did not appear to increase with dose escalation. The majority of AEs were mild in severity.

Pharmacokinetic Parameters	Day 1	Day 14
AUC_{0-24} (ng*hr/mL)	9185 ± 4397.8 [n=8]	27130 ± 10300 [n=8]
AUC_{0-t} (ng*hr/mL)	8150 (60.4) [n=8]	75560 (29.9) [n=8]
C_{max} (ng/mL)	2423 (136.1) [n=8]	5971 (99.2) [n=8]
T_{max} (hr)	1.017 (0.50, 2.04) [n=8]	1.019 (0.52, 2.03) [n=8]
RA,AUC	NA	3.077 ± 0.48037 [n=8]

Table 5: Plasma Pantothenate Pharmacokinetic Parameters in MD.

Headache was the most frequently reported AE with a total of 4 reports by 4 (13%) subjects among the SAD, with two subjects following 500 mg, and one subject each following 2000 mg and 5000 mg doses. One (13%) subject reported a headache in the MD. Of these, two events were mild in severity and three were moderate severity. Three subjects received paracetamol and one subject received an ice bag for headache resolution. The investigator considered two headaches to be probably/possibly related to calcium pantothenate and three unlikely/unrelated.

Two subjects experienced laboratory-related AEs. The first was a SAD 500 mg subject with a severe AE of increased blood CPK secondary to heat exposure that occurred approximately eight days following a single dose of 500 mg calcium pantothenate. The increased CPK AE resolved approximately a week after onset and was considered by the investigator to be unlikely related or unrelated to calcium pantothenate. The second subject (SAD 2000 mg) had a mild AE of decreased absolute neutrophil count that occurred approximately one day following a single dose of 2000 mg calcium pantothenate. The event resolved approximately 17 days after onset. The investigator considered the decreased neutrophil AE to be probably/possibly related to calcium pantothenate.

All remaining AEs were reported by 2 (6%) or fewer subjects each among the SAD and all AEs in the MD were experienced by 1 (13%) subject each. Of these AEs, the investigator considered the following to be at least possibly related to calcium pantothenate (treatment in parentheses): decreased neutrophil count (SAD 2000 mg), abdominal discomfort, anorectal discomfort, diarrhea, postural dizziness, discolored feces (SAD 5000 mg, Fasted); and pollakiuria (SAD 1000 mg). The remaining were determined to be unrelated to calcium pantothenate. All AEs resolved by end of study. There were no remarkable trends noted in the remaining laboratory, vital sign, ECG, or physical examination assessments during this study.

	SAD						**MD**
Adverse Events*	**500 mg N=8**	**1000 mg N=8**	**2000 mg N=8**	**5000 mg, fasted N=8**	**5000 mg, fed N=8**	**Total N=32**	**2000 mg N=8**
No. of Subjects With TEAEs	4 (50%)	2 (25%)	3 (38%)	1 (13%)	0 (0%)	10 (31%)	3 (38%)
Gastrointestinal disorders							
Abdominal discomfort	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)	1 (3%)	1 (13%)
Anorectal discomfort	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)	1 (3%)	0 (0%)
Diarrhea	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)	1 (3%)	0 (0%)
Feces discolored	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)	1 (3%)	0 (0%)
Nausea	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)
Vomiting	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)
General disorders and administration site conditions							
Vessel puncture site hemorrhage	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)
Vessel puncture site pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)
Injury, poisoning and procedural complications							
Skin abrasion	1 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Laboratory Investigations							
Blood creatine phosphokinase increased	1 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Neutrophil count decreased	0 (0%)	0 (0%)	1 (13%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)

Musculoskeletal and connective tissue disorders							
Back pain	0 (0%)	0 (0%)	2 (25%)	0 (0%)	0 (0%)	2 (6%)	0 (0%)
Nervous system disorders							
Dizziness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)
Dizziness postural	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)	1 (3%)	0 (0%)
Headache	2 (25%)	0 (0%)	1 (13%)	1 (13%)	0 (0%)	4 (13%)	1 (13%)
Renal and urinary disorders							
Nephrolithiasis	1 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Pollakiuria	0 (0%)	1 (13%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Respiratory, thoracic and mediastinal disorders							
Productive cough	0 (0%)	1 (13%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)

*AEs are classified according to System Organ Class and Preferred Term of MedDRA® Version 21.0
TEAEs = Treatment-emergent adverse events

Table 6: Treatment-Emergent Adverse Events.

Discussion

To our knowledge, this is the first study to evaluate the detailed PK of high-dose orally administered calcium pantothenate in healthy adults. The findings support previous work that demonstrated overall low toxicity of high doses. Animal toxicity tests with D-calcium pantothenate in mice, rats, dogs, and monkeys demonstrated very high acute oral lethal dose (LD50) values in mice and rats of greater than 10,000 mg/kg, with lethal doses producing death by respiratory failure [11,12]. Case reports and older non-controlled studies in humans indicated that the administration of very high doses of calcium or sodium pantothenate up to 10 g/day, in some cases over years, was safe and well tolerated, with most AEs being diarrhea and gastrointestinal symptoms [13,16]. One study in 41 children with attention deficit disorder showed significant increases in serum aspartate transaminase levels in 17 children after 12 weeks of multivitamin therapy which included calcium pantothenate 1200 mg/day and niacinamide 3 g/day [17]. However, it is not known to what extent this observation may have been due to the niacinamide component of the supplement, given the known effects of that compound on liver enzymes. Our finding that doses above 2000 mg did not result in increased exposure was a unique result of this investigation, as was the previously undocumented food effect.

Our study has several shortcomings which should be noted. First, vitamin B5 can be considered ubiquitous and is found in a normal diet. There was no dietary monitoring or control of dietary intake of vitamin B5 during the study, and while pre-study baseline levels of pantothenate were collected, the PK data were not adjusted based on these values. Exposure PK parameter estimates may be more variable as a result, as well as the half-lives estimated. The AUC%extrap estimated for all cohorts following a single dose ranged between 33-67%. This may be the result of the vitamin that is taken in with food, hence the concentration measured is not necessarily related to the administered drug itself and the long elimination half-life is a resultant artefact. This is also consistent with the effective half-life calculated based on the observed accumulation which was shorter than the more prolonged observed t½, potentially reflecting the underlying ubiquitous

concentrations. Therefore, all Kel-dependent PK parameters should be interpreted with caution. Further, the study enrolled healthy adults only. We therefore cannot draw conclusions on the response in individuals with conditions affecting absorption, distribution, metabolism and excretion of Vitamin B5. The lack of dose-dependent adverse events in our study suggests the overall safety of high dose administration.

Conclusion

Following orally administered calcium pantothenate in healthy adults across a dose range of 500 mg to 5000 mg, calcium pantothenate overall exposure increased dose-proportionally from 500 to 2000 mg and less than dose-proportionally from 2000 to 5000 mg. The highest exposure was observed at the 2000 mg dose. The consumption of food with the administration of 5000 mg calcium pantothenate resulted in an increase in overall exposure and delayed peak concentration by approximately 2 hours. A 2000 mg daily dose was tolerated and resulted in steady state by Day 14. These results could impact development of therapeutics for diseases associated with coenzyme-A deficiency that may include supplementation with oral calcium pantothenate.

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Conflict of Interest

AW, AS and RE are employed by CoA Therapeutics Inc,. and own shares in its parent company BridgeBio Pharma. SR and US, are employees of Eidos Therapeutics and own shares in BridgeBio Pharma. DG is a consultant to BridgeBio Pharma and owns shares in the company. SV and JK hold shares in CoA Therapeutics.

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