An Open-Label, Single-Dose, Crossover Study of the Pharmacokinetics and Metabolism of Two Oral Formulations of 1-Octanol in Patients with Essential Tremor

Fatta B. Nahab · Loretta Wittevrangel · Dominic Ippolito · Camilo Toro · George J Grimes · Judith Starling · Gopal Potti · Dietrich Haubenberger · Daniel Bowen · Peter Buchwald · Chuanhui Dong · Daniel Kalowitz · Mark Hallett

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Abstract Existing therapeutic options for management of essential tremor are frequently limited by poor efficacy and adverse effects. Likely the most potent tremor suppressant used is ethanol, although its use is prohibitive due to a brief

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F. B. Nahab (✉) · C. Dong
Department of Neurology,
University of Miami Miller School of Medicine,
Miami, FL 33136, USA
e-mail: fnahab@med.miami.edu

L. Wittevrangel · D. Ippolito · C. Toro · D. Haubenberger · M. Hallett
Human Motor Control Section, Medical Neurology Branch,
NINDS/NIH,
Bethesda, MD 20892, USA

G. J. Grimes · J. Starling · G. Potti
Pharmaceutical Development Section, NIH,
Bethesda, MD 20892, USA

D. Haubenberger
Department of Neurology, Medical University of Vienna,
Vienna, Austria

D. Bowen
Wake Forest University,
Winston-Salem, NC 27106, USA

P. Buchwald
Department of Molecular and Cellular Pharmacology,
University of Miami Miller School of Medicine,
Miami, FL 33136, USA

D. Kalowitz
Albert Einstein College of Medicine,
Bronx, NY 10461, USA

therapeutic window, and the obvious implications of excessive alcohol use. Longer-chain alcohols have been shown to suppress tremor in harmaline animal models, and appear to be safe and well tolerated in 2 prior studies in humans. Here we report on the findings of a phase I/II study of 1-octanol designed to explore pharmacokinetics, efficacy, and safety. The most significant finding was the identification of octanoic acid as the product of rapid 1-octanol metabolism. Furthermore, the temporal profile of efficacy closely matches the plasma concentration of octanoic acid. Therefore, these findings identify a novel class of compound (e.g., carboxylic acids) with tremor suppressive properties in ET. Administration of 1-octanol also appears to be safe based on various measures collected. Essential tremor (ET) is the most common tremor disorder, with tremors occurring during static posturing or movement. These tremors are known to briefly improve in many cases after alcohol (ethanol) consumption. Two previous studies of a longer chain alcohol, 1-octanol, have demonstrated longer duration tremor-suppressive effects without the occurrence of intoxication. The aim of this study was to characterize the pharmacokinetics of 1-octanol and its primary metabolite octanoic acid using two formulations, along with additional safety and efficacy measures. Participants with proven ethanol-responsive ET were recruited into 1 of 2 parts: (part A) a dose escalation study (1–64 mg/kg; n=4), and (part B) a fixed dose (64 mg/kg; n=10) balanced, open-label crossover design. Two participants in part B then completed an exploratory part C evaluating 128 mg/kg. Plasma samples were collected at 10 intervals during a 6-hour period postingestion. Efficacy was assessed using spirometry, whereas safety was assessed with electrocardiograms, vital signs, adverse effects surveys, and an intoxication assessment. Plasma concentrations of 1-octanol were detect-

able at low levels whereas octanoic acid (OA) concentrations were approximately 100-fold higher. The half-life of OA was 87.6 minutes. This was matched by a clinical reduction in tremor severity of 32% at 90 minutes, assessed using spirometry. The safety profile was favorable, with the most commonly reported adverse effect being dysgeusia (38%). Early detection and higher plasma concentrations of OA are a product of rapid metabolism of 1-octanol. OA pharmacokinetics mirrored the timing of clinical improvement. These findings provide preliminary evidence for a new class of compound that may be effective in the treatment of ET.

Keywords 1-Octanol · Octanoic acid · Essential tremor · Alcohol · Therapeutics · Spirometry

Introduction

Essential tremor (ET) is a progressive neurological disorder causing postural and kinetic tremors of the hands, head, voice, and legs. The leading hypothesis for ET pathophysiology is an unmasking of spontaneous oscillations originating in neurons of the inferior olive [1]. A helpful diagnostic feature of ET is the observed reduction of tremor amplitude after ethanol intake with preservation of the tremor frequency. Of those with ET who consume alcoholic beverages and are aware of their tremor effects, 74% report having ethanol-responsive tremors [2]. The mechanism by which ethanol provides therapeutic benefit is unknown, although animal data suggest tremor reduction is mediated by decreased synchronization of inferior olive oscillations [3]. Unfortunately, the tremor-suppression effects of ethanol occur at a dose close to its effective dose (ED₅₀) for intoxication, or the dose at which 50% of individuals experience this effect [4].

Similar to ethanol, 1-octanol has been found to block low-threshold calcium channels in the inferior olive using a rat model of ET [3]. Based on this background, Bushara et al. [5] undertook an initial placebo-controlled single dose (1 mg/kg) trial of 1-octanol in 12 patients with ET. Their finding showed 1-octanol was well tolerated, with tremor benefits observed for 15 to 90 minutes postdose compared with placebo. A second open-label dose escalation study was designed to evaluate the tolerability of higher oral doses of 1-octanol and found no evidence of intoxication or serious adverse effects up to 64 mg/kg [6]. Efficacy was found at all dosages, and a trend toward a dose response was noted. Both studies attempted to characterize pharmacokinetics, but were unable to detect 1-octanol. The inability to detect 1-octanol led us to speculate that rapid metabolism to a daughter compound may be occurring. Metabolism of octanol is mediated by various enzymes, with alcohol dehydrogenase (ADH) playing a major role. This pathway involves the conversion of octanol to its corresponding aldehyde (octanal)

before forming octanoic acid; however, under *in vitro* incubation of octanol with ADH, octanal disappears rapidly (<5 min) leaving only octanoic acid [7]. This led us to hypothesize that octanoic acid was the most likely stable metabolite. Both prior studies also used a capsule formulation that could break open as participants attempted to swallow the pills, leading to various reports of an unpleasant taste (dysgeusia) associated with the 1-octanol. Concern of the feasibility of future blinded clinical trials led us to develop an alternate formulation for testing.

The objective of this trial was to characterize the pharmacokinetics of 1-octanol and its hypothesized primary metabolite, octanoic acid, using two different formulations. We also assessed efficacy, tolerability, and safety in this sample of patients with ethanol-responsive ET.

Methods

Patients

Since the mechanism of action of 1-octanol is likely similar to that of ethanol, we recruited ET patients who reported an improvement in tremor with alcohol. Additional inclusion criteria included: limb-predominant tremors, ability to safely stop and remain off all medications used to treat ET for at least 4 half-lives, willingness to abstain from ethanol and caffeine intake for at least 48 hours prior to and during the study participation, and ability to fast for periods of as much as 12 hours during the study.

Patients were excluded if they had significant abnormalities other than tremor on neurological examination, past or present alcohol abuse or dependence, acute or chronic severe medical conditions (such as renal failure), hepatic failure or lung disease, taking primidone (due to its extended half-life), other acute or chronic medications potentially influencing hepatic metabolism or central nervous system function, inability to temporarily discontinue tremor medication for the duration of the study, significant abnormalities on baseline screening laboratory tests, and cognitive impairment preventing informed consent. We also excluded patients younger than 21 years of age, women who were pregnant or lactating, anyone who did not wish to take a potentially intoxicating drug, and patients from far East Asian or Native American descent (due to their likelihood for possessing variant alleles of the genes for alcohol metabolism that could result in slower metabolism and potentially increase their sensitivity to alcohols and their metabolites).

Study Design

Participants were recruited from the clinic, the local community, and through various internet-based resources.

Eligible subjects were brought to the National Institutes of Health Clinical Center in Bethesda, Maryland. Written informed consent was obtained from all participants for this protocol that was approved by the institutional review board of the National Institute of Neurological Disorders and Stroke (Study Identifier: NCT00102596) and the Food and Drug Administration under investigational new drug status (IND#61864 and #68751).

The initial screening visit included a complete medical history and neurological examination, laboratory screening (complete blood count with differential, electrolytes, renal function, liver function, ethanol level, coagulation profile, urinalysis, urine pregnancy test), and electrocardiogram. The tremor examination was videotaped and severity assessed with the Fahn-Tolosa-Marin Tremor Rating Scale [8] and digital spiral analysis using a pen-based Wacom tablet (Wacom Intuos 3 Model PTZ-930, Wacom Technology Corp., Vancouver, WA). Then patients judged to have ET based on consensus criteria [9] underwent an ethanol challenge to assess the degree of tremorresponsiveness. Subjects could receive up to three 50 ml servings of ethanol (40% by volume) at 30-minute intervals. Tremor amplitude was assessed at 15-minute intervals by spirometry time series analysis and portions of the tremor rating scale. Patients demonstrating ethanol-responsive tremors based on clinical assessment and reduction in tremor amplitudes on spirometry were then eligible to participate in the inpatient study.

The inpatient study consisted of 2 parts (i.e., parts A and B). In part A, a dose escalation (1–64 mg/kg) study was used to validate the assay, and in part B, a fixed dose (64 mg/kg) balanced, open-label crossover study was used to assess pharmacodynamics of the 2-drug formulations for the study. In both study parts, subjects fasted overnight for 6 hours before receiving 1-octanol at 6 AM. Four patients participated in part A, and 10 patients in part B. Sample size estimation was based on ethanol studies due to the lack of 1-octanol pharmacokinetic data. At the completion of these studies, and we added an exploratory part C using the same study design as part B, but evaluating a 128 mg/kg dose in 2 patients who participated in part B.

We evaluated 2 formulations for this study. The first formulation, produced by the Pharmaceutical Development section of the National Institutes of Health, consisted of 1-octanol adsorbed to microcrystalline cellulose, NF (Avicel PH 102, FMC Corp., Philadelphia, PA), and fine particle silica (Sipernat 50S, Evonik Degussa Corp., Parsippany, NJ) and encapsulated in 50 mg and 250 mg dosages. This formulation (CEL) was used in the two prior studies of 1-octanol [5, 6]. A second formulation consisted of a soft-gel capsule containing 1-octanol embedded in soybean oil at 50 mg and 800 mg dosages (Best Formulations Inc, City of Industry, CA). This formulation (SOY) was developed due

to concerns about the instability of the CEL formulation during swallowing and the potentially greater likelihood for participants to report dysgeusia if the capsule fractured prematurely.

Plasma samples were collected from a peripherally inserted central catheter at 10 time points during a 6-hour period after 1-octanol ingestion (Table 1). Because subjects received a weight-adjusted dose, the number of pills for each individual varied. Time of ingestion was defined as the time-point when the first pill was swallowed. After collection, blood samples were coded, centrifuged, and cooled on an hourly basis, then aliquoted and stored at -80°C until shipped to the laboratory for processing. Samples were batch analyzed with high-pressure liquid chromatography with mass spectrometry using standard methods. Based on pre-clinical validation studies, the assay linear range of detection was 20 to 1000 ng/ml for both 1-octanol and octanoic acid.

Efficacy was assessed by tremor amplitude change via spirometry time series analysis using a commercially available digitizing tablet, connected to a laptop. Subjects were asked to draw Archimedes spirals in between the lines of a 5-loop template spiral with each hand at multiple time points throughout the observation period. Tremor amplitudes were calculated at the tremor frequency peak after fast Fourier transformation of the spirometry time series using published methodology [10, 11].

Safety measures included electrocardiograms, vital signs, and adverse effects survey [12]. Potential signs of intoxication were assessed using an alcohol intoxication scale; six different domains were potentially affected by intoxication (sedation, speech, finger tapping, finger-to-nose test, gait, tandem gait) and were examined, with each domain graded from 0 to 4 (0=normal and 4=maximum intoxication). Assessments were made at baseline and at regular intervals after treatment (Table 1). At the completion of the inpatient testing, peripherally inserted central catheter lines were removed and participants were discharged after a final safety assessment. An outpatient telephone follow-up was conducted 1 week after discharge to assess for remote adverse effects.

Statistical Analysis

Pharmacokinetic analyses of the data for 1-octanol and octanoic acid, were performed using standard noncompartmental analyses with Phoenix WinNonlin 6.0 (Pharsight Corp., St. Louis, MO). Nominal times were used in all calculations; all actual times were close enough not to cause any significant changes in any of the pharmacokinetics (PK) estimates. Values for maximum plasma concentration, C_{max} , and the time to reach maximum concentration, t_{max} , were obtained directly from the concentration-time data.

Table 1 (A) Summary timeline for procedures taking place during an inpatient drugday. (B) Study design summary showing dose escalation schedule for (Part A), and fixed doses for (Part B) and (Part C). For (Part A), subjects were randomized to receive a single formulation of 1-octanol (CEL/SOY) for the dose escalation phase (1–32 mg/kg) followed by both formulations at 64 mg/kg. Subjects in (Part B) and (Part C) similarly received both formulations on separate study days in random order, with intervening washout periods

A	Baseline	0 min	5 min	15 min	20 min	30 min	45 min	60 min	70 min	90 min	100 min	120 min	130 min	150 min	160 min	180 min	210 min	240 min	270 min	300 min	360 min
Screening labs	X																				
Pregnancy test	X	±																			
EKG*	X		X								X										
Octanol given†		X																			
Vital signs*	X	X	X	X	X	X	X	X	X			X				X					X
Spirography*		X	X	X	X	X	X	X	X	X		X		X		X	X				X
AE Survey*		X	X	X	X	X	X	X	X	X		X		X		X	X	X			X
Intoxication scale*		X				X	X	X	X	X		X		X		X	X	X			X
Plasma sample			X		X		X		X		X		X		X		X		X		X

B	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Part A	1 mg/kg	8 mg/kg	16 mg/kg	32 mg/kg	Washout	64 mg/kg	Washout	64 mg/kg	Washout
Part B	64 mg/kg	Washout	64 mg/kg	Washout					
Part C	128 mg/kg	Washout	128 mg/kg	Washout					

*Procedures that were also performed on washout days

† 1-octanol dose administered based on (B) (bottom section of the table)

EKG = electrocardiogram; min = minutes

Terminal elimination rate constants (λ_z) were obtained using log-linear regression on the terminal phase, as selected by the default WinNonlin (Pharsight Corp.) procedure that uses the largest number of last points with nonzero concentrations that maximize the adjusted r^2 of the corresponding regression [13]. Elimination half-lives were then calculated using the standard $t_{1/2} = \ln(2)/\lambda_z$ relationship. Areas under the curve (AUCs) were calculated using the linear trapezoidal method. The area under the curve to last concentration (AUC_{0-t}) was calculated from time 0 to time of the last measurable concentration (C_{pL}). The area under the curve to time infinity ($AUC_{0-\infty}$) was calculated as $AUC_{0-\infty} = AUC_{0-t} + C_{pL}/\lambda_z$. The apparent volume of distribution (V_d/F) based on the terminal phase was calculated as $V_d/F = \text{dose}/(\lambda_z \times AUC_{0-\infty})$, and the apparent clearance CL/F was calculated as $\text{dose}/AUC_{0-\infty}$. Because 1-octanol concentrations were undetectable or very low for the majority of patients, no V_d or CL calculations were done for 1-octanol and a set of formal V_d or CL estimates were made for the acid metabolite assuming full conversion of the parent compound. Data for each individual were fitted separately, and averages $\pm$ standard deviations were calculated for each group. Concentration data below the lower limit of quantitation (20 ng/ml for both compounds) were considered as zero.

For statistical analysis of efficacy, the spiral tremor amplitude of the right hand at each timepoint after drug administration was normalized to each baseline, which was recorded on each study day before drug administration. A repeated measures 2 factor analysis of variance model was performed to assess for differences related to time (each time point) and formulation (CEL/SOY). As baseline was set to 1 without variance across subjects, only time points after administration were included in the model. Missing datapoints were imputed using the “last observation carried forward” method. The Kolmogorov-Smirnov test was applied to test for normal distribution. In case of significant effects, post-hoc comparisons were made using paired sample t tests. All comparisons were corrected for multiple testing (Bonferroni). A statistical level of $p < 0.05$ was considered significant. Electrocardiogram parameters (heart rate, PR interval, and QTc) collected at multiple time points (baseline, 15 minutes, 100 minutes, and 24 hours) were compared using a mixed-effects model. Descriptive statistics were performed for all reported adverse effects.

Role of the Funding Source

The intramural program of the National Institute of Neurological Disorders and Stroke provided primary funding for this work. A collaborative research and development agreement between National Institute of Neurological Disorders and Stroke and Ariston Pharmaceuticals provided

expertise and funding for assay development, sample testing, and support for a research coordinator.

Results

Twenty-one patients were screened and 14 patients completed the study (Fig. 1). Table 2 provides a summary of patient demographics. The study population consisted of varying disease severities, with the vast majority reporting a family history of ET, and all patients reported alcohol-responsive tremors because this was a criterion for enrollment. Tremor alcohol-responsiveness was clinically confirmed during the screening visit for all subjects enrolled.

The assays that were used detected both 1-octanol and octanoic acid successfully. Only very low 1-octanol concentrations were present in all participants, and clearly quantifiable levels (>50 ng/ml) were only present in a minority of participants in the 2 highest-dose groups (64 and 128 mg/kg). Conversely, octanoic acid concentrations were detectable and quantifiable at all time points. In general, 1-octanol levels paralleled octanoic acid levels (Fig. 2), but because of the large number of 1-octanol data below the lower limit of quantitation at all dose levels, no quantitatively reliable analyses could be performed for 1-octanol. Concentrations, AUC, and $C_{\max}$ values were approximately 100-fold higher for the metabolite (octanoic acid) than the parent compound (1-octanol), suggesting that the effects of 1-octanol were mediated almost entirely by its metabolite. Furthermore, the metabolite appeared quickly in the plasma, with detectable octanoic acid concentrations seen within 5 minutes of oral ingestion in most individuals, and remained at quantifiable levels in all participants at the last sampling time (at 6 hours).

Because 1-octanol concentrations were so low for the majority of participants, meaningful PK analysis could be performed only for octanoic acid (Table 3). The dose escalation part of the study (1–32 mg/kg) also contained

Fig. 1 Patient flow profile

Table 2 Baseline demographic characteristics

Mean age (Standard deviation)	68.1 (8.1)
Gender, n (%)	
Male	9 (60%)
Female	6 (40%)
Mean height, cm (Standard deviation)	169.6 (12.0)
Mean weight, kg (Standard deviation)	82.9 (20.1)
Mean body mass index (Standard deviation)	28.6 (4.7)
Mean age of onset, years (Standard deviation)	39.5 (18.6)
Mean disease duration, years (Standard deviation)	28.7 (17.2)
History of alcohol-responsive tremors, n (%)	15 (100%)
Mean # servings of alcohol (50 ml of 40% ethanol) required for tremor response	2.1 (0.3)
Family history of Essential tremor, n (%)	13 (87%)
Mean tremor rating scale score (Standard deviation) ¹	41.6 (17.6)

¹ Data for patients 1–5 not available

n = number of patients

few subjects and lacked a crossover comparison between the two formulations (CEL/SOY). Based on these restrictions, we conducted our analysis on the 64 mg/kg dose (n=12) that was well defined and comparable between the two formulations. Nonetheless, the pharmacokinetics were linear for the dose range studied (1–128 mg/kg), with both $C_{\max}$ and AUC values of octanoic acid increasingly linear with higher doses (r^2 of 0.954 [CEL] and 0.995 [SOY]; p values of 0.00015 and 0.0000007, respectively)(Fig. 3).

Maximum concentrations of octanoic acid were reached for the 64 mg/kg dose at 72.9 and 81.7 minutes for CEL and SOY, respectively, and absorption (plus metabolism) is similar for the two formulations being slightly faster for CEL. 1-octanol also seems to reach its peak blood level at approximately 100 minutes, although this finding is limited by the very low levels. Bioavailability is similar but slightly better for SOY at 64 mg/kg, in which the AUC_{6h} and $C_{\max}$ ratios for SOY and CEL are 142.5% and 170.0%, respectively ($p < 0.01$; Figs. 2 and 3). For all doses greater than 4 mg/kg, in which the elimination phase could be

meaningfully evaluated, elimination showed no dose-dependence, also confirming an essentially linear PK (e.g., the elimination constant λ_z has a value of around 0.01 min^{-1}). The average elimination half-life ($t_{1/2}$) of all doses and formulations is 87.6 minutes for octanoic acid.

Assessment of the clinical response using spirometry time course analysis compared every study timepoint for participants to their own baseline tremor severity of the right hand (Fig. 4). Normalized spirometry tremor scores were normally distributed. The repeated measures of analysis of variance showed significant changes from baseline across time ($F_{3,014}$; $p = 0.006$). Post-hoc comparisons showed a significant reduction in tremor scores at 90 ($p = 0.002$), 120 ($p = 0.006$), 150 ($p = 0.03$), and 180 minutes ($p = 0.003$). We found no significant differences based on formulation type ($p = 0.8$) and no significant interaction between time and formulation ($p = 0.3$). We also found no rebound tremor up to 24-hours postdose.

Assessment of potential cardiovascular effects of 1-octanol using baseline and postdose electrocardiograms found

Fig. 2 Concentration time profiles for 1-octanol (dashed lines) and octanoic (oct.) acid (solid lines) for both formulations (CEL: green; SOY: blue) after a 64-mg/kg dose. Data are mean $\pm$ standard error of the mean for all subjects (n=12; balanced crossover design); note that compared to octanoic acid, octanol concentrations are shown on a magnified scale (right vertical axis)

Table 3 Summary of PK parameters for octanoic acid for all doses and formulations

Form.	Dose (mg/kg)	N	C _{max} (ng/mL)	T _{max} (min)	AUC _{6h} (ng min/mL)	λ _z (1/min)	T _{1/2} (min)	AUC _∞ (ng min/mL)
CEL	1	2	385.7	20.0	46231.0	0.00154	450.3	94938.2
CEL	4	1	925.0	70.0	133859.2	0.01070	64.8	140889.1
CEL	8	2	2820.0	20.0	213535.5	0.00901	85.6	222307.1
CEL	16	2	3829.8	12.5	312371.2	0.00825	89.1	323631.3
CEL	32	3	4809.2	45.0	761165.0	0.01316	61.1	792446.1
CEL	64	12	9143.4	72.9	1398164.9	0.00733	102.7	1620687.7
CEL	128	2	25019.2	32.5	4810868.2	0.00500	148.3	5564892.8
SOY	1	3	607.3	36.7	39714.5	0.00150	558.4	87366.7
SOY	4	1	1999.3	45.0	112874.8	0.00566	122.4	117814.1
SOY	8	3	3434.7	53.3	247018.6	0.00874	86.3	256278.7
SOY	16	2	8360.7	60.0	543195.6	0.01168	67.9	550814.6
SOY	32	3	9737.0	93.3	954747.0	0.01111	69.2	980749.0
SOY	64	12	15548.2	81.7	1992316.9	0.01221	62.0	2078459.6
SOY	128	2	30070.8	100.0	4616032.5	0.01160	180.6	5581177.2

λ_z = Terminal elimination rate constant; AUC_∞ = area under the curve to time infinity; AUC_{6h} = area under the curve at 6-hours; C_{max} = Maximum plasma concentration; CEL = Cellulose formulation; Form. = formulation; min = minutes; N = number of subjects; PK = Pharmacokinetics; SOY = Soy formulation; T_{max} = Time to maximum concentration; T_{1/2} = Elimination half-life

transient reductions in the heart rate at the 15-minute (−4.2 bpm; $p=0.02$) and 100-minute (−3.7 bpm; $p=0.04$) timepoints (Table 4). No clinically significant bradycardia or changes in blood pressure, respiratory rate, or temperature were observed. The adverse effects profile was similar to prior reports with dysgeusia being the most common, reported by 38% of participants with varying descriptions of bitter, acidic, sweet, or metallic flavors. Reports of dysgeusia were more common with the CEL formulation compared with SOY (62.5% vs 37.5%, respectively). Other adverse effects are summarized in Table 5. No significant signs of intoxication were observed on clinical evaluation,

with only a single participant at a single time point (64 mg/kg, 240 minutes) during the entire study having transient, mild gait instability. No significant adverse effects were reported during the telephone survey 1 week after discharge. No serious adverse effects were drug-related. Two unrelated serious adverse events included 1 patient who was withdrawn from the study after developing flu symptoms after study day 1 and having spontaneous resolution with a typical course ensuing for 2 days, while a second patient accidentally slipped and sustained a fractured rib during the 1-week follow-up period after completion of inpatient participation.

Fig. 3 Total octanoic acid area under the concentration (AUC_{6h}) as a function of 1-octanol dose. Data are mean ± standard error of the mean for all subjects at all dose levels in each formulation; the number of subjects at each dose level are as those summarized in Table 3

Fig. 4 Spirography mean tremor amplitudes for right hand vs time post-octanol dose (64 mg/kg). Time course of tremor improvement shows a maximal reduction by 90 to 180 minutes, independent of the formulation (CEL/SOY) and persistent effects beyond the study time window for the SOY formulation. Error bars represent standard error. *Statistical significance ($p<0.05$) for each time-point vs baseline

Discussion

Historic references to ET as a “benign tremor” have been supplanted by recent work showing nearly three quarters of affected individuals experience significant disability, decreased productivity and reduced quality of life [14]. Despite the diversity of nonsurgical pharmacologic options, adverse effects are common and 25 to 55% of patients gain no benefit from medical therapy [14]. Arguably the most effective treatment, ethanol is known to have potent anti-tremor properties [4], although routine use is prohibitive due to the high risk of intoxication and the serious medical, social, and legal consequences of chronic alcohol use.

1-octanol has been proposed as a potentially safer alternative alcohol due to its generally recognized as safe status by the Food and Drug Administration [15] and the lower effective dose required to reduce harmaline-induced tremor by 50% (ED50) of 0.26 mg/kg compared with 100 mg/kg of ethanol in animal models [3, 16]. Although animal data of 1-octanol and ethanol show similar acute toxicology profiles, 1-octanol is approximately 5 to 6 times less potent in inducing intoxication [17–19]. These data would suggest an approximate 1-octanol ED50 for intoxication of 5.8 g for a single dose, close to our 64 mg/kg dosing, although we found no signs of intoxication at this level or in the 2 subjects we studied at 128 mg/kg.

The most significant outcome of this work is the confirmation that 1-octanol is rapidly absorbed and metab-

Table 5 Adverse events summary, n (%)

Body system/organ class	
CNS and PNS disorders	
Headache	5 (24%)
Sedation	2 (10%)
Dizziness	2 (10%)
Worsening tremor	2 (10%)
Numbness	1 (5%)
Vertigo	1 (5%)
Gastrointestinal	
Dysgeusia	8 (38%)
Heartburn	5 (24%)
Gas/bloating	5 (24%)
Nausea	4 (19%)
Dry mouth	4 (19%)
Constipation	3 (14%)
Diarrhea	2 (10%)
Cardiovascular	
Hypotension	1 (5%)
Lightheadedness	1 (5%)
Respiratory	
Cough	2 (10%)
Psychiatric disorders	
Anxiety	2 (10%)
Insomnia	1 (5%)
Visual disorders	
Blurred vision	1 (5%)
Dry eyes	1 (5%)
Skin disorders	
Sweating	1 (5%)

Table 4 Electrocardiogram summary (n=15)

Parameter	Least square mean* (SE)	Significance (p)
Heart rate		
Baseline	70.8 (2.9)	Reference
15 min	66.6 (2.7)	0.02
100 min	67.1 (2.7)	0.04
24 h	72.4 (2.7)	0.38
PR Interval (ms)		
Baseline	168.8 (6.6)	Reference
15 min	172.8 (6.2)	0.31
100 min	171.6 (6.2)	0.48
24 h	168.6 (6.2)	0.97
QTc (ms)		
Baseline	433.8 (8.4)	Reference
15 min	436.5 (7.4)	0.67
100 min	433.0 (7.4)	0.89
24 h	437.4 (7.5)	0.58

*Adjusted for age, sex, period and formulation.

h = hours, min = minutes; ms = milliseconds; n = number of subjects; SE = Standard error

olized to octanoic acid. Octanol is a typical substrate for ADH3, which is highly expressed in gastric mucosa and helps to explain the rapid appearance of octanoic acid observed here [20]. Based on the pharmacokinetic data and spirometry, the anti-tremor effects appear to be almost entirely mediated by octanoic acid, although the open-label design of our study and the administration of 1-octanol limits us from making this definitive conclusion. This is significant for a number of reasons. First, octanoic acid has a bioavailability of nearly 100% [21]. Second, reaching the plasma concentrations of octanoic acid achieved in this study would require a lower oral dose of octanoic acid than that of 1-octanol. Finally, octanoic acid also has Food and Drug Administration generally recognized as safe status and human dietary consumption of up to 710 mg/kg is considered safe [22].

The improvements in tremors we identified at the 64 mg/kg dosages were significant, with a mean improvement in tremor severity of 32.2% at 90 minutes and a sustained

benefit (33.2%) at 6 hours (SOY formulation). Furthermore, these improvements were clinically evident and confirmed by patient observations. The findings also underscore the importance of using an unbiased objective measure of tremor that is highly sensitive and does not rely on highly trained raters to ensure validity [10].

The safety profile of 1-octanol in this study was consistent with prior reports [5, 6] and showed 1-octanol to be well tolerated, with mild side effects, such as headache, gastrointestinal discomfort, and nausea in less than a quarter of participants. These symptoms, along with dysgeusia, are likely to be formulation-related and may be minimized by future formulations. Methodological shortcomings of this study include the small sample size, open-label design, and indirect evidence for the therapeutic effects of octanoic acid. Future studies should build on this initial work to evaluate the efficacy and safety of direct administration of octanoic acid, as well as the long-term safety and efficacy of multiple daily dose administrations for the management of ET.

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Full conflict of interest disclosure is available in the [electronic supplementary material](#) for this article.

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