Treatment of Essential Tremor with Long-Chain Alcohols: Still Experimental or Ready for Prime Time?

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Abstract

Aim: To review current literature on long-chain alcohols and their derivatives as novel pharmacotherapy for the treatment of essential tremor (ET).

Background: Currently available and recommended pharmacotherapies for ET are often limited by suboptimal treatment effects, frequent adverse effects, and drug interactions. While ethanol is reported to profoundly decrease tremor severity in the majority of patients with ET, preclinical experience suggests that long-chain alcohols such as 1-octanol might lead to a comparable tremor reduction without ethanol’s typical side effects of sedation and intoxication. Here, we review the literature on the first clinical trials on 1-octanol and its metabolite octanoic acid (OA) for the treatment of ET.

Methods: The literature on preclinical and clinical trials on long-chain alcohols as well as OA was reviewed and summarized, and an outlook given on next phases of development.

Discussion: 1-octanol was demonstrated to be safe and effective in a double-blind, placebo-controlled low-dose trial, and open-label data showed excellent tolerability and dose-dependent efficacy up to 128 mg/kg. Despite 1-octanol’s efficacy, its future viability as an effective therapy is limited by its pharmacological properties that require large volumes to be orally administered. Pharmacokinetic data indicate that OA is the active metabolite of 1-octanol. Preclinical efficacy data for OA are positive, and human pilot data demonstrated excellent safety as well as efficacy in secondary outcome measures of tremor amplitudes. OA also has more favorable pharmacological properties for drug delivery; hence, OA may be worth developing as a pharmaceutical.

Keywords: Essential tremor, alcohol, ethanol, octanol, octanoic-acid, harmaline-model

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Introduction

Essential tremor (ET) is a common movement disorder with a prevalence in the general population between 0.4% and 3.9%. ET is a slowly progressive disease with 73% of patients describing disabilities in multiple functional domains including eating, drinking, writing, and body care.

Since there is currently no curative therapy available for ET, medical agents including propranolol and primidone as well as deep brain stimulation of the ventral intermediate nucleus (VIM) are symptomatic therapeutic options. However, the clinical effects of these first-line drugs are often limited by contraindications and intolerable side effects, particularly in elderly patients, and many patients are not keen on surgery.

Ethanol and essential tremor

One characteristic observation in ET is that up to 74% of affected subjects report a significant reduction in tremor intensity after the administration of small amounts of ethanol. It should be noted that this observation is based on subjective data only, while objective data on the ethanol response in ET is scarce. In a study by Knudsen et al., a standardized oral ethanol challenge led to an improvement of up to 50% of hand tremor scores in 25 patients, which lasted up to 3 h. It was also demonstrated by the same group that after ethanol, ataxia scores and number of missteps during tandem gait improved equally in patients with ET, suggesting a beneficial effect of ethanol in ET patients beyond the actual tremor.

The evidence for a central effect of ethanol was demonstrated to be mediated by the central nervous system (CNS), as an effect was seen after systemic intravenous administration, without effect after intrarterial perfusion in a vascularity isolated limb of patients with ET. Furthermore, the tremor-reducing effect on the central component was demonstrated to be specific for ethanol, as diazepam showed no effect. Furthermore, this finding demonstrated that ethanol acted specifically on a central tremor oscillator at plasma ethanol levels of 0.05 g/dL, independent of effects mediated through relaxation or sedation seen with diazepam.

Several hypotheses exist regarding the mechanism of ethanol’s effect in ET. First, ethanol has been suggested to decrease the neuronal firing rate of the inferior olive (IO) and may therefore lead to a reduction in hypersynchronous bursting activity within Mollaret's triangle connecting the red nucleus, the IO, and the cerebellum, with further propagation along the cerebello-thalamo-cortical loop. There are two possible derangements. First, this mechanism is thought to be mediated through modulation of low-threshold calcium channels in the IO that are responsible for rhythmic cellular firing.

There can be hyperfunctioning of the low-threshold calcium channel in the inferior olivary cells leading to oscillatory neuronal activity. Notably, ethanol in low doses has been reported to increase T-type currents of low-threshold calcium channels; however, at toxic levels data show ethanol is blocking these channels. While the relevance of low-threshold calcium channels has been demonstrated in the harmaline model of ET, the role in humans remains to be elucidated, as in humans lesions affecting the efferent cerebellar pathways (such as strokes) might abolish tremor in ET patients, but no “curative” lesions affecting the IO complex have been reported so far.

Contrary to the hypothesis of ethanol as a depressor of neuronal IO firing, a study using different methods of anesthesia by Rogers et al. suggested that the depressing effect might in fact be due to the specific anesthesia used in the original experiment by Harris and Sinclair (urethane), as ethanol under this varying anesthesia condition actually led to an increase in the IO single-unit firing rate.

Second, the neuronal rhythmic discharges within the IO may be hypersynchronized by electrical coupling mediated through gap junctions. These gap junctions connect and therefore electrically couple dendritic spines in synaptic glomeruli within the IO, which are thought to be central for the IO’s oscillatory activity. Gamma-aminobutyric acid (GABA)ergic terminals in the synaptic glomeruli have shown to decrease the extent of electric coupling. By blocking connexin 36, a crucial gap junction protein within the IO, mice still develop harmaline-induced tremor although with decreased tremor coherence. This suggests that the profound tremor-reducing effect of gap junction blockers such as mefloquine in harmonic mice may act via different gap junctions, not containing connexin 36.

Furthermore, ethanol’s agonism on GABA receptors has been implicated as a correlate of its tremor-suppressing properties. GABA is the main inhibitory neurotransmitter, with GABA receptors being expressed either synaptically (90%) or extrasynaptically (10%). Synaptic receptors mediate phasic inhibition, whereas tonic inhibition is mediated via extrasynaptic receptors, which are thought to be physiologically activated by “overspill” of synthetically released GABA. GABA receptors form pentamers containing two alpha, two beta, and either one gamma or one delta subunit. The majority of GABA receptors contain a gamma subunit, are expressed synaptically, and are benzodiazepine sensitive. Receptors containing a delta subunit are mainly expressed extrasynaptically and are nonsensitive to benzodiazepines but in contrast show a very high sensitivity.
Long-chain Alcohols in ET
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Alcohols ranging from methanol (CH₂O) to decanol (C₁₀H₂₂O) were first studied using an in vitro model of guinea-pig IO neurons, where octanol was described to be a potent antagonist of IO low-threshold calcium channels. In a further step, several octanol isomers, including 1-octanol, were first studied in vivo using the harmaline-induced rodent model of ET. All isomers, at varying effective doses, demonstrated a potent effect in reducing harmaline-induced tremor. In a comparative study on 1-octanol and 1-heptanol, both long-chain alcohols, reduced harmaline-induced tremor in mice at a dose of 350 mg/kg after intraperitoneal administration, with 1-octanol exhibiting a superior efficacy profile than 1-heptanol due to a longer duration of the effect.

1-Octanol: preclinical evidence

The eight-chain alcohol 1-octanol is hypothesized to be metabolized by octanol dehydrogenase, a member of the alcohol dehydrogenase family of enzymes, to an aldehyde and then a carboxylic acid that is either oxidized completely to carbon dioxide and water or excreted as an ether-glucuronide after direct conjugation with glucuronic acid.

1-Octanol has been demonstrated to block the low-threshold calcium channel in the IO and thalamus in vivo. The maximum tolerated dose preclinically in harmaline mice after intraperitoneal administration using the straight-wire test was 1,000 mg/kg. The Food and Drug Administration (FDA) food additive safety profile on 1-octanol lists lethal acute toxicity levels in rodents (LD₅₀) ranging from 1,790 to 15,000 mg/kg.

1-Octanol: clinical trials

1-Octanol was first chosen for clinical trials due to its superior efficacy and safety profile in animal model testing, and the fact that 1 mg/kg dosing was considered to be safe in humans, as defined by the Council of Europe. 1-Octanol is approved as a food flavoring substance by the FDA.

The first clinical trial in ET was conducted using a low dose of 1 mg/kg in 12 patients. A single oral dose of 1-octanol showed a moderate effect in reducing tremor up to 90 min after administration, measured by accelerometry, using a double-blind, placebo-controlled design. 1-Octanol was well tolerated and safe at this dosage. Three patients (two in the octanol group, one in the placebo group) complained of headaches occurring after the completion of the study. In all three patients, the headache lasted for less than 2 h and responded to acetaminophen. No changes in vital signs or liver function tests were detected. No signs of intoxication were observed.

The second protocol using 1-octanol was an open-label dose escalation study to find the maximal tolerated oral dose of 1-octanol. Octanol doses were escalated up to 64 mg/kg without evidence of intoxication, though subjects had a sensation of sedation at maximal doses. Efficacy was found at all dosages, and a trend toward a dose response was noted. Safety profiles showed no significant adverse events, with some mild side effects. Two subjects had a self-limited headache following drug administration, four subjects noted a taste associated with the drug approximately 1 h after ingestion, four subjects described a transient mild asthenia without signs of intoxication, and two subjects had a prolonged feeling of lethargy at 64 mg/kg lasting for several hours. Single reports of nausea, dry mouth, calcium oxalate crystals in the urine, and urinary tract...
infections were present, and in the case of the last two were likely unrelated. No laboratory abnormalities or electrocardiogram (EKG) changes were noted.40

The most recent 1-octanol protocol (clinicaltrials.gov ID: NCT00102596) investigated the pharmacokinetic properties of two different oral formulations of 1-octanol in 15 patients with ET.41 The first formulation consisted of 1-octanol adsorbed to microcrystalline cellulose and fine particle silica and encapsulated; the second formulation consisted of a soft-gel capsule containing 1-octanol embedded in soybean oil.41

This protocol was designed as a three-phase unblinded inpatient study of adults with ET receiving weight-adjusted oral dosages of two different formulations of 1-octanol in a crossover fashion. Phase 1 of the study was designed to develop octanol and OA detection assays using high-performance liquid chromatography. Five subjects in phase 1 received daily escalating dosages (1–64 mg/kg) of a single 1-octanol formulation. In phase 2, 10 subjects received one of the two formulations at 64 mg/kg during two inpatient days separated by one washout-day. In phase 3, two patients received a high-dose challenge of both formulations of 1-octanol (128 mg/kg).

Plasma concentrations of both 1-octanol and OA were detectable as early as 5-min post dose. While OA concentrations showed a dose response, 1-octanol remained at very low basal levels until the 64 mg/kg dose. The OA plasma half-life was 73.6 min. In phase 3 of the study, after the administration of a high dose of 1-octanol (128 mg/kg), observed OA plasma levels followed a linear relation compared with lower doses of 1-octanol. These findings suggested that 1-octanol is rapidly converted to OA, which might then act as the active metabolite. Efficacy was measured using objective digital tremor spiral analysis.42 Spiral tremor measurements showed a 32% reduction in tremor amplitudes at 90 min with significant tremor improvement up to 180 min after administration. The safety profile of 1-octanol up to 128 mg/kg resembled prior studies with non-serious side effects being mild and self-limiting. The most frequent adverse event was taste change, which was reported by eight subjects (38%), followed by headache, heartburn, and bloating (each five subjects, 24%). Nausea and dry mouth were reported by four subjects (19%), and three subjects reported constipation (14%). Two serious adverse events were not related to the study drug. Again, no signs of intoxication were noted at either dose level.

**Octanoic acid**

OA (synonym: caprylic acid) is a fatty acid with an eight-carbon chain, which has been shown to inhibit gap junction permeability in cultured rat astrocytes.43 Whether this observation is relevant to explain a potential effect in ET remains uncertain, as it is not known whether OA also blocks neuronal gap junctions. OA occurs naturally in palm and coconut oils, as well as in human and bovine milk, and is part of commercially available nutritional supplements (Caprinol®, Capryl®). After absorption in the intestinal mucosa and entering the portal venous system, the hepatic metabolism of OA involves catabolism via β-oxidation to acetyl coenzyme A (CoA) with subsequent entry into the Krebs cycle. Extrahepatic metabolism of OA involves oxidation into CO₂ with extrahepatic tissues.44,45

The FDA has registered OA as a food additive and adjuvant of food products, and assigned it “GRAS” (Generally Recognized as Safe) status. Currently, OA is mainly used as a food and cosmetic additive as well as an assessment method of gastric emptying (¹³C OA breath test). The Council of Europe lists OA as a flavoring substance with an upper limit of 50 mg/kg in food.46 Orally administered OA shows a bioavailability of nearly 100%.47 In the rat, OA permeated the blood–brain barrier, with 94% of peripherally injected OA being measurable in the brain.48 To our knowledge, there are no data in the literature on the elimination profile of OA from the CNS. In a study of acute oral toxicity in rats, the LD₅₀ was 10,080 mg/kg.49

**Octanoic acid: experience from human exposure**

There is considerable data available on human exposure of OA. In humans, according to a single-dose administration paradigm of medium-chain fatty acids, a dietary consumption of up to 710 mg/kg was considered safe.50 In a clinical trial including a control group of healthy volunteers, a total dose of 3,600 mg OA was administered via intraduodenal infusion, and no clinical side effects were reported.51 OA was furthermore studied as a component of a ketogenic diet as a treatment strategy in children with intractable epilepsy, with a duration of chronic administration for up to 2 years.52,53 An OA-containing diet was administered on a daily basis as an emulation with the goal that 60% of the daily energy requirement was supplied by the diet. Fifty children were included in the study, with 44 children tolerating the diet. Reported side effects were diarrhea and abdominal pain, which were alleviated by temporary dose reduction or intake together with food. “Optimal” plasma levels of OA intended by the authors was a target of 90 μg/mL peak plasma concentration (Cₘₐₓ), with the actual measured Cₘₐₓ values ranging from 98.2 to 258.9 μg/mL. Compared with the available pharmacokinetic data on OA in essential tremor, these plasma levels were 75–200 times higher than the Cₘₐₓ we measured in the ET trial using 1-octanol. The dose vs. plasma concentration relation was suggested to follow a linear relationship.52

Further human data on OA stem from a study administering OA as a formula to six premature infants. OA was administered orally in doses ranging from 1.3 to 1.7 g/kg/d (mean 1.5 ± 0.2 g/kg/d) via a medium-chain triglyceride diet over a period of at least 10 days. The goal of this study was to investigate the metabolism of medium-chain triglycerides in infants. The authors demonstrated the conversion of OA into long-chain saturated fatty acids. The study did not mention any adverse events.54 In a study of 23 cachectic patients, OA given orally at a dose of 2.8 g daily over 2 weeks increased appetite scores, body weight, and levels of total serum protein and albumin, with no negative impacts on fasting glucose, total cholesterol, or triglycerides. The aim of the study was to investigate the effect of OA on the orexigenic hormone ghrelin, and demonstrated that OA led to an increase in acyl ghrelin.55 High levels of OA were measured in patients with a deficiency of medium-chain acyl-CoA dehydrogenase (OMIM...
#607008), an autosomal recessive inherited disorder of infancy and early childhood leading to metabolic acidosis, hypoglycemia, lethargy, coma, and if left unrecognized led to death in 25% of patients during their first crisis.\textsuperscript{56,57} Regarding potential drug interactions, it has been shown that high levels of OA can displace warfarin and non-steroidal anti-inflammatory agents from albumin binding in human serum.\textsuperscript{58}

**Octanoic acid in ET: preclinical evidence**

Because of OA’s presumed role as 1-octanol’s primary metabolite and its biochemical properties, OA itself was hypothesized to act as a potential therapeutic agent in ET. In the harmaline-induced mouse-model of ET, OA showed a dose-dependent effect in reducing tremor intensities, starting at 300 mg/kg administered intraperitoneally with a maximum tolerated dose of 1,500 mg/kg. At therapeutic doses no toxicity was observed, especially no signs of sedation or intoxication.\textsuperscript{59}

**Octanoic acid: first experience in ET**

The aim of the first study of OA in ET was to examine the safety and efficacy of a single oral OA dose in a double-blind, randomized, placebo-controlled, crossover design (NCT00848172).\textsuperscript{59} Nineteen patients with ethanol-responsive ET were included in the protocol. All subjects received a dose that was defined as being safe according to available toxicity data (4 mg/kg) and were monitored closely during the total inpatient study phase of 3 days (day 0, baseline; days 1–2, active study days). OA and placebo were administered on consecutive study days in a randomized sequence. The primary outcome measure for this study was the effect on tremor power of the dominant hand, 80 min after administration of the study substance compared with placebo. Tremor power was measured using accelerometry with loading to test the central tremor component. Secondary outcome measures included recordings of tremor power as measured by accelerometry at multiple other time points up to 300 min after administration. The change in tremor severity documented by digital spiral analysis, safety assessment (laboratory testing, documentation of vital signs, adverse events questionnaire, and intoxication scale), and pharmacokinetic sampling acted as a further secondary outcome parameter.

Efficacy endpoints measured with tremor accelerometry did not meet the primary endpoint (reduced tremor power of the dominant hand 80 min after administration, compared with placebo). However, secondary efficacy measures showed a significant benefit over placebo at later time points, starting at 150 min. At the last observational time point, 300 min, there was still a significant reduction in tremor power compared with baseline.

Pharmacokinetic analysis of OA showed a \( t_{\text{max}} \) at 72.8 min, a relatively large volume of distribution (389 L), and an elimination half-life of 83.5 min. The elimination did not entirely follow first-order kinetics, suggesting the presence of a second compartment. The mean \( C_{\text{max}} \) after administration of 4 mg/kg was 1,288.4 ng/mL, which is close to the \( C_{\text{max}} \) of OA that was measured after the administration of 4 mg/kg of 1-octanol.

Safety analysis showed that the dose was safe and well tolerated. There were no serious adverse events related to OA, with non-serious adverse effects being mild, self-limiting, and equally present after OA and placebo. Two serious adverse events were classified as not related to OA (food poisoning with isolated troponin I elevation after placebo, and bleeding from the insertion site of a peripherally inserted central venous catheter after premature removal of pressure dressing). There were no significant abnormalities noted on vital signs, EKG, or laboratory measures throughout the study.

**Summary and outlook**

With pharmacotherapy in ET often being limited by insufficient efficacy, intolerable side effects, and potential drug interactions, novel treatments for ET are strongly needed. While the ethanol effect in ET is still not fully understood and currently under investigation, it is clear that the majority of patients experience a clinically significant effect of tremor reduction even after low doses of ethanol consumption, often exceeding the effects of pharmacological treatments such as propranolol and primidone.

With the detailed mechanism of effect of ethanol in ET still to be determined, promising preclinical data led to the further development of long-chain alcohols as potential treatment agents in ET. It is however important to point out that ethanol shows different (lower) affinity to target structures than longer-chain alcohols such as 1-octanol. It is therefore not necessarily the case that ethanol and 1-octanol act via the same mechanism. Also, 1-octanol might act not via one, but multiple mechanisms (i.e., blockage of gap junction, T-type calcium channels, GABA-receptor interaction).

The fact that the 1-octanol and OA studies so far required participants to exhibit a beneficial response to ethanol therefore stems from a debatable assumption of similar pathways facilitating the effect. It is however also important to point out that the current concept on the proportion of ET patients responding beneficially to ethanol, or not, is likely outdated, as these data stem from purely subjective reports. Objective data from larger-scale populations are still pending, to investigate whether differences in ethanol response can be objectively delineated and whether therefore a concept of two separate ET endophenotypes based on ethanol response can be sustained. However, in the light of the current diagnostic uncertainty and significant disagreement in the field on the “core” ET phenotype, a limitation to objective ethanol responders might be justified for early stage clinical trials to achieve a cohort exhibiting a more homogeneous phenotype.

With three clinical trials available on efficacy, safety, and pharmacokinetic properties of 1-octanol, the main results can be summarized as 1-octanol being safe and well tolerated in doses up to 128 mg/kg. The most common adverse event was mild and transient dysgeusia, with patients reporting a distinct taste of orange peel, which was to be expected as 1-octanol as natural flavoring substance is present in orange peel. In terms of efficacy, all studies demonstrated a significant treatment effect of 1-octanol, though it should be noted that only the first, low-dose study was a double-blind, placebo-controlled design. One major finding of the 1-octanol trials was the detection of OA as an active metabolite with a significant plasma response after the administration of 1-octanol. The feasibility of 1-octanol was furthermore questioned, not only because the distinct taste would make
sufficient blinding challenging, but also because of the relatively large volumes to be administered orally at doses of 64 and 128 mg/kg; even with the formulation using the highest 1-octanol concentration (gel capsule containing 800 mg 1-octanol), a patient weighing 78 kg who took part in the highest dose group of 128 mg/kg had to swallow 12 capsules as a one-time dose.

OA itself showed an excellent safety and efficacy profile in preclinical testing and during human exposure as a nutritional agent, even at high doses and in vulnerable subjects such as preterm infants. While OA was well tolerated in a pilot study using a low dose (4 mg/kg), the primary efficacy outcome was not met, with OA not being different from placebo in reducing tremor 80 min after administration. However, the study design included several secondary efficacy outcomes, which showed a significant effect on tremor at later time points. The observation of a peak in plasma levels at 73 min being dissociated from a clinical effect manifesting at 150 min and later, in conjunction with an elimination profile compatible with a second compartment, suggests that the second compartment is likely the CNS, where the clinical effect is manifesting after distribution of the compound across the blood–brain barrier, potentially explaining the lag of a clinical efficacy peak following the plasma peak. While the effect was evident using highly sensitive tremor accelerometry, other methods better reflecting daily-life activities such as digital spiral analysis were not different between OA and placebo. As this was a low-dose study, it was assumed that the effect at 4 mg/kg was still small and not yet translating into a clinically relevant benefit. Therefore, a dose escalation study, with the goal of defining a maximum tolerated dose with doses up to 128 mg/kg, was initiated (NCT01468948), with the results at the time of this review still pending. Further studies are needed on the effect of OA when administered continuously (e.g., twice daily, three times daily, etc.), on the further characterization of OA’s pharmacokinetic profile at higher doses, and the optimization of the drug’s formulation.

To conclude, despite its efficacy and safety, 1-octanol itself does not seem a feasible candidate for further development due to the relatively large volumes to be administered when formulated in capsules for oral administration, as well the finding of OA as the active metabolite. Although OA’s mechanism of action in ET is still unknown, the therapeutic potential of OA in ET can be considered as significant, due to promising preclinical and early-stage clinical trial data. However, a clinically relevant effect translating into a reduced burden of tremor in patients’ daily lives still remains to be demonstrated, and additional phase 2 data on safety and efficacy in a long-term administration setting are necessary, in order to keep OA moving forward towards prime time.

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