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Reducing the Rate of Rise of Plasma Concentrations Improves the CNS Side-Effect Profile of Lacosamide

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Background

- Lacosamide immediate release (IR), Vimpat®, is approved for the treatment of partial onset seizures.
- Dose limiting adverse events associated with lacosamide IR include central nervous system (CNS) effects such as headache and dizziness.
- Lacosamide IR has a rapid rate of rise in plasma concentration (t_{max} ~1 h), and we hypothesized that reducing the initial rate of rise in plasma concentration may reduce CNS adverse events.

Objective

- The objective of these studies was to correlate the rate of rise in lacosamide plasma concentrations with CNS side effects, measured as an impairment of motor coordination in rodents using the rotarod.

Methods

Mouse Pharmacokinetic (PK) and Rotarod Pharmacology Studies

The PK profile and the effects on rotarod performance of lacosamide was determined following single oral doses in mice.

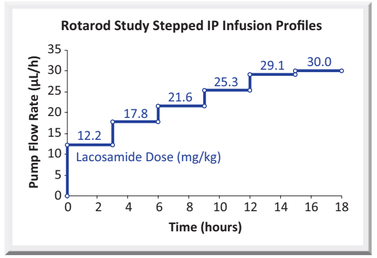
Male CD-1 mice (n=4/group/timepoint, Charles River, Germany) were administered a single dose of 30 or 90 mg/kg lacosamide in 0.9% saline by oral gavage. Plasma and brain samples were collected at 0.08, 0.25, 0.5, 1, 2, 6, 8 and 12 h post-dose.

Male CD-1 mice (Charles River, Germany) were trained on the accelerating rotarod (0-40 rpm over 5 min) one day before drug administration and testing. On the test day, mice (n=13-15/group) were administered vehicle (0.9% saline) or a single oral dose of 3, 10, 30, 60 or 90 mg/kg lacosamide. Accelerating rotarod testing was conducted 5, 15, 30 and 60 min post-dose. Data is presented as mean ± SEM.

Rat Rotarod Pharmacology Studies

The effect on rotarod performance of different rates of rise to achieve the same lacosamide plasma C_{max} was determined in rats.

Male Sprague Dawley rats (Charles River, Germany) were used in these studies. All main study rats in both Study 1 and Study 2 below were initially trained on the accelerating rotarod (0-40 rpm over 5 min) and all rats that met the rotarod training criterion (at least 120 s in 2 consecutive trials) underwent iPRECIO pump implantation surgery 1-2 days later. Following a 3-day recovery period from the implantation surgery, all rats were tested on the accelerating rotarod for baseline measurements and were allocated to treatment groups (N=8-10/group) such that the mean time on the rotarod was not significantly different between groups within a study. Dose levels and infusion rates were modelled based on PK modeling from a previous PK study in rats (see Figure for simulation). The dose of lacosamide for the IP bolus injection in Study 2 was selected to produce a C_{max} similar to that obtained following continuous IP infusion of lacosamide for 16 h described in Study 1.



Study 1: one day after baseline rotarod assessments, continuous 18 h IP infusions of vehicle (20% N-Methyl-2-pyrrolidone [NMP] in water) or lacosamide via the iPRECIO pump were conducted. A stepped infusion protocol with six different infusion rates (programmed to increase every 3 h, see Figure) which produced a linear increase in lacosamide plasma concentration before reaching C_{max} (total dose infused over 18 h = 122 mg/kg). At the end of infusion, rats were tested on the accelerating rotarod.

Study 2: one day after baseline rotarod assessments, rats received a single IP bolus injection of either vehicle (20% NMP in water) or 19 mg/kg lacosamide, 1 h before being tested on the accelerating rotarod.

After rotarod testing, rats were euthanized by CO_2 asphyxiation and plasma was collected from each rat via cardiac puncture.

A parallel group of 4 animals received the same lacosamide infusion regimen or IP bolus injection but instead of rotarod testing, serial plasma samples were collected from these animals via tail vein (PK satellites).

Bioanalytical Analysis

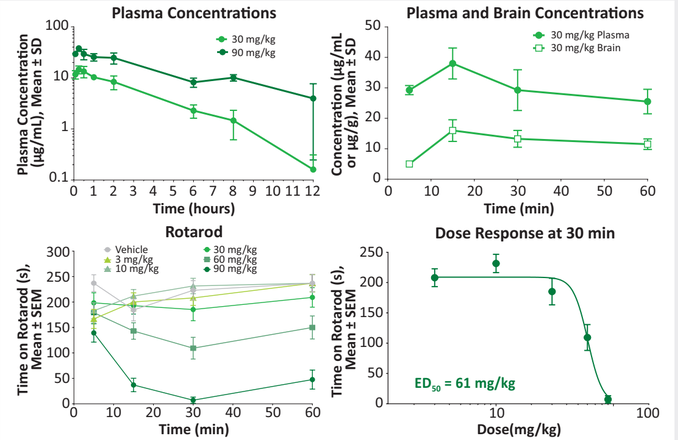
For all mouse and rats studies, samples were stored frozen until analyzed by LC/MS/MS. Where appropriate, standard PK parameters were estimated using WinNonLin 6.3 Phoenix Build 6.3.0.395. All lacosamide concentration graphs are presented as mean ± SD.

Rotarod Analysis

Rotarod performance (time to fall) was compared to baseline within animals and the percent change from baseline for each animal was presented as the mean (± SEM) for each treatment condition.

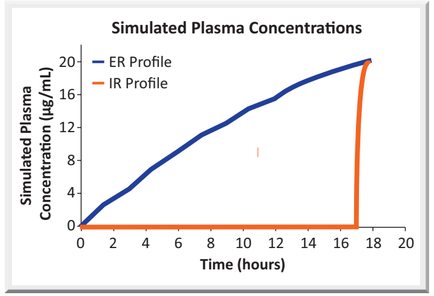
The effect of an IP bolus and a stepped infusion of lacosamide on the percent change from baseline was compared using a Student's t-test with significance reported at the P<0.05 level.

Mouse PK and Rotarod Results



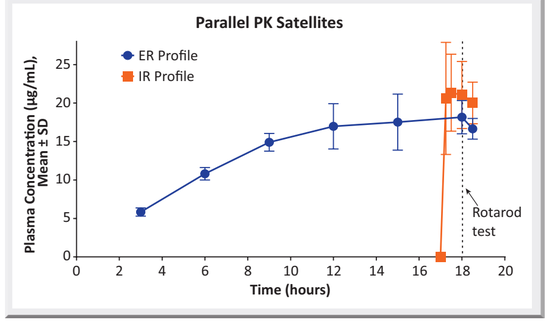
- Oral lacosamide produced a dose-dependent impairment of rotarod performance in mice with an ED_{50} of 61 mg/kg.
- Peak impairment occurred at 30 min post dose and near complete impairment was produced by 90 mg/kg.
- Time course of lacosamide levels in plasma and brain were very similar, with t_{max} in both compartments at 15 min post dose.
- Plasma exposure was dose-proportional. $AUC_{0-\infty}$ (µg•h/mL) was 50 and 202 µg•h/mL for 30 and 90 mg/kg, respectively. AUC/dose was similar for both dose levels (1.66 and 1.88 respectively).
- Mean plasma and brain levels at 90 mg/kg, at t_{max}, were 38 µg/mL and 16 µg/g, respectively.
- Mean brain:plasma ratios ranged from 0.17 at 5 min to 0.42-0.46 at 15-60 min post-dose.

Rat PK Simulations

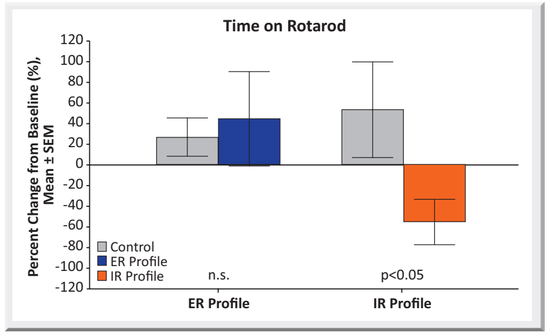


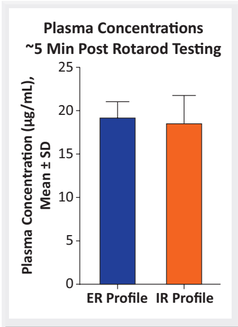
- Target plasma concentrations of lacosamide for the rat rotarod study were selected based on published data in mice and rats wherein impairments on the rotarod were reported following single IP or oral doses at concentrations of 20–40 µg/mL (Vimpat Ref.)
- Infusion rates were simulated to produce a linear increase in plasma concentrations throughout a 18 hour infusion and doses were selected to yield plasma lacosamide concentrations of 20 µg/mL at the end of the infusion based on pharmacokinetic data obtained from previous Adamas PK studies.

Rat PK and Rotarod Results



Parameter	ER Profile	IR Profile	ER/IR ratio
C_{max} (µg/mL)	20	22	0.9
$Slope_{0\text{-}C_{max}}$ (µg/mL/h)	1.4	62	0.02
Total Dose (mg/kg)	122	19	6.4
$AUC_{0\text{-}18.5\,h}$ (µg•h/mL)	234	29	8.1





- In rats, the 18 h infusion (ER Profile) and single IP bolus dose of lacosamide (IR Profile) produced similar terminal blood levels and C_{max} in PK satellite animals.
- The single IP bolus dose produced a significant deficit in rotarod performance (55.0 ± 22.5% decrease from baseline in the treated group compared to a 53.6 ± 45.9% increase from baseline in vehicle animal).
- Slow rise infusion of lacosamide to a similar C_{max} did not produce any deficit in rotarod performance.
- The slow ER-like profile resulted in a 6.4 fold increase in dose and 8.1 fold increase in exposure without significant CNS impairment.

Conclusions

- Our initial studies in the mouse indicated a clear dose-dependent impairment of rotarod performance in a plasma range relevant to those reported to produce clinical adverse effects with Lacosamide IR.
- Delivery of lacosamide by implanted iPRECIO pump and IP bolus injection allowed us to model a >30-fold slower rise to equivalent C_{max} in rats. t_{max} was longer when administered by continuous IP infusion (15 h; range 12-18 h) compared to IP bolus (0.75 h; range 0.25-1.5 h).
- Slowing the rate of rise of plasma levels significantly reduced the CNS side effects of lacosamide, as measured by impairment of the ability to stay on the accelerating rotarod.
- Therapeutic strategies that reduce the rate of rise of lacosamide plasma concentrations may result in improved tolerability and may enable higher doses for the treatment of partial onset seizures.

Reference

Vimpat® (lacosamide) Injection and Tablets: Application Number NDA 022-253 and 022-254].

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