Epilepsy Research 149 (2019) 13–16

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Short communication

Modeling and simulation for the evaluation of dose adaptation rules of intravenous lacosamide in children

Julia Winkler[a,b,*], Rik Schoemaker[a,b], Armel Stockis[c]

[a] SGS Exprimo, Generaal de Wittelaan 19A b5, 2800, Mechelen, Belgium
[b] Current affiliation: Occams, Malandolaan 10, 1187 HE, Amstelveen, Netherlands
[c] UCB Pharma, Chemin du Foriest, 1420, Braine-l'Alleud, Belgium

ARTICLE INFO

Keywords:
Oral
NONMEM
Pharmacokinetics
Epilepsy

ABSTRACT

A combined adult and pediatric population pharmacokinetic model including covariate effects was developed; simulations were subsequently performed to guide intravenous pediatric dosing adaptations. Two pharmacokinetic trials with sparse blood sampling were conducted in children with epilepsy and two trials in healthy adults with serial blood sampling. Lacosamide plasma concentration–time data were available from 43 healthy adults (18–45 years of age; body weight 50–101 kg; $n = 1735$ concentration vs time records), and from 79 children with epilepsy (6 months–17 years of age; body weight 6–76 kg; $n = 402$ concentration vs time records), with 14, 22, 25 and 18 participants in age groups < 2 years, 2 to < 6 years, 6 to < 12 years and 12 to < 18 years, respectively. A two-compartment population pharmacokinetic model was developed using nonlinear mixed effects modeling. Plasma clearance was scaled using a fixed allometric exponent on body weight, while central volume of distribution used a freely estimated allometric exponent. The model-based pharmacokinetic predictions suggested that there is no need to adapt the recommendations regarding intravenous infusion durations in children compared with adults.

1. Introduction

Lacosamide (tablet and oral solution, LCM) is approved as adjunctive therapy and monotherapy for adults and children aged ≥4 years with focal epilepsy (UCB Pharma, 2018a,b). Lacosamide intravenous (IV) infusion is currently approved for adults (≥16 years of age) in the United States (US) and for adults and children (≥4 years of age) in the European Union (EU) (UCB Pharma, 2018a,b). The solution for IV infusion is injected over a period of 15–60 min twice daily. Conversion to and from oral and IV administration can be done directly without titration. The total daily dose and dosing regimen should be maintained. The maximum recommended dose is determined according to body weight band. In the EU, the approved maximum maintenance dose when prescribed as adjunctive therapy is 12 mg/kg/day for pediatric patients weighing < 20 kg, 10 mg/kg/day for pediatric patients weighing 20 to < 30 kg, 8 mg/kg/day for pediatric patients weighing 30 to < 50 kg, and 400 mg/day for pediatric patients weighing ≥50 kg and for adults; and as monotherapy is 12 mg/kg/day for pediatric patients weighing < 40 kg, 10 mg/kg/day for pediatric patients weighing 40 kg to < 50 kg, and 600 mg/day for pediatric patients weighing ≥50 kg and for adults. In the US, the approved maximum maintenance dose when prescribed as adjunctive or monotherapy is 400 mg/day.

Clinical pharmacology studies in healthy young and elderly participants and in patients with focal epilepsy, established the overall absorption, distribution, metabolism, and elimination properties of LCM. Data from these trials have indicated that LCM demonstrates high oral bioavailability, linear and dose-proportional pharmacokinetics (PK), low inter- and intra-individual variability, and low potential for drug–drug interactions. These results are important because they establish the predictable PK profile of LCM and help inform clinician decisions to achieve the desired drug response profile (Cawello et al., 2014).

Previously, a population PK model for oral LCM had been developed in children with epilepsy from 1 month to 17 years of age using nonlinear mixed effects modeling based on two early phase clinical trials (SP0847, clinicaltrials.gov identifier: NCT00938431; SP1047, EudraCT number: 2014-002629-36) (Winkler et al., 2015). Trial SP0847 was a Phase II, open-label, dose-titration study investigating LCM oral

Abbreviations: AED, antiepileptic drug; AUCτ, area under the plasma curve over a dosing interval; C_{max}, steady-state peak plasma concentration; FOCE-I, first order conditional estimation with interaction; IV, intravenous; OFV, objective function value; PK, pharmacokinetic(s)

* Corresponding author.
E-mail addresses: julia.winkler@occams.com (J. Winkler), info@occams.com (R. Schoemaker), armel.stockis@ucb.com (A. Stockis).

https://doi.org/10.1016/j.eplepsyres.2018.10.011
Received 21 May 2018; Received in revised form 14 September 2018; Accepted 23 October 2018
Available online 26 October 2018
0920-1211/

Table 1
Pharmacokinetic parameter estimates for the final LCM model in healthy adults and children with epilepsy using body weight-dependent CL/F and V/F.

Parameter (units)	Population estimate	95% confidence interval	Inter-individual variability (CV)
CL/F (L/h)	2.57	2.43 / 2.71	23.0%
V_c/F (L)	28.2	24.5 / 32.0	35.6%
K_a (1/h)	4.05	3.28 / 4.82	70.9%
V_p (L)	13.1	10.6 / 15.7	55%
Q (L/h)	39.1	33.6 / 44.5	
F	1.01	0.989 / 1.030	3.8%
Allometric scaling exponent on CL	0.75 (fixed)		
Allometric scaling exponent on V_c	0.722	0.647 / 0.796	
D_1	0.401	0.327 / 0.476	58.0%
Fold-change in CL with CBZ co-administration	1.50	1.33 / 1.71	
Fold-change in CL with PB co-administration	2.59	2.32 / 2.89	
Fold-change in CL with PHT co-administration	1.56	1.17 / 2.08	
Proportional residual error (SD/mean), peds	0.250	0.213 / 0.287	
Proportional residual error (SD/mean), adults	0.129	0.112 / 0.147	

CBZ = carbamazepine, CL = plasma clearance; CV = coefficient of variation; D_1 = duration of zero-order oral absorption; F = bioavailability; K_a = absorption rate constant; PB = phenobarbital, peds = pediatric subjects, PHT = phenytoin, Q = inter-compartmental clearance; V_c = central volume of distribution; V_p = peripheral volume of distribution. Full equation for CL = exp((log(Θ5) + Θ8 * log(WT/70) + CBZ * Θ13 + PB * Θ14 + PHT * Θ15) + ETA1).
Full equation for V_c = exp((log(Θ6) + Θ12 * log(WT/70)) + ETA2).
Θ5 = population estimate of CL, Θ6 = population estimate of V_c, Θ8 = allometric scaling factor for CL (0.75 fixed), Θ12 = allometric scaling factor for V_c (freely estimated), Θ13 = estimate of CBZ coadministration effect, Θ14 = estimate of PB coadministration effect, Θ15 = estimate of PHT coadministration effect, ETA1 = IIV on CL, ETA2 = IIV on V_c.

solution (titrated from 2 mg/kg/day to up to 12 mg/kg/day) as adjunctive therapy in 47 children (1 month to 17 years of age) (Ferreira et al., 2015). Patients with uncontrolled focal seizures on a stable dose regimen of one to three AEDs were enrolled. Trial SP1047 was an open-label study to investigate the pharmacokinetics of LCM (tablet or oral solution) in 32 children (1 month to 17 years of age) who were prescribed LCM for epilepsy. Patients had to be on a stable LCM dose regimen as prescribed by a physician for at least 7 days before study entry with no missed doses within 3 days before PK sampling. In both studies, sparse blood samples were taken at prespecified time points for plasma LCM determination.

Together with these two pediatric trials, the present report incorporated data from two crossover bioavailability/bioequivalence studies in healthy adults with administration of both oral and IV infusions of different duration (Cawello et al., 2012). Study SP645 involved 16 participants who received single doses of LCM 200 mg orally and as a 15-min infusion, and plasma concentration was measured over time up to 72 h after each administration; study SP658 included 27 participants who received single doses of LCM 200 mg orally and as 30-min and 60-min infusion, respectively (Cawello et al., 2012).

The objective of this analysis was to develop a population PK model for LCM in healthy adults and in children with epilepsy using nonlinear mixed effects modeling, in order to predict pediatric IV PK profiles and to perform simulations of different dosing regimens of IV infusions of LCM in children with epilepsy and to assess the need for dosing adaptations.

2. Methods

A PK analysis using the population approach was conducted to determine the population PK parameters of LCM in healthy adults and in children with epilepsy after IV infusion and oral dosing with tablet/solution, respectively. The analyses were performed using NONMEM software (version 7.2.0, ICON Development Solutions, Ellicott City, MD, USA) with first order conditional estimation with interaction (FOCE-I). Influence of body weight on clearance was included *a priori* as a structural part of the model. From a previous analysis co-administration of inducing AEDs (carbamazepine, phenobarbital and phenytoin) was associated with a faster LCM clearance and was therefore included. After successful model evaluation, a pediatric dataset with 100 individuals per body weight category and infusion duration, ranging from 5 to 75 kg (in increments of 5 kg) and from 15 to 60 min (in increments of 15 min), respectively, as well as with and without co-administration of inducer AED was simulated (total of $N = 24{,}000$ individuals). Subsequently, the final model was used to predict different LCM IV dosing regimens (dosing by weight at 8, 10 and 12 mg/kg/day, and constant dose of 400 or 600 mg/day), with varying infusion duration (15–60 min) to propose dose adaptation rules in children with epilepsy.

3. Results

Lacosamide plasma concentration–time data were available from 43 healthy adult participants (18–45 years of age, body weight 50–101 kg) with serial blood sampling ($n = 1735$ concentration vs time records), and from 79 children (body weight 6–76 kg) with infrequent blood sampling ($n = 402$ concentration vs time records), with 14, 22, 25 and 18 participants in age groups < 2 years, 2 to < 6 years, 6 to < 12 years and 12 to < 18 years, respectively.

Initial development of the population PK model started in the adult dataset with a one-compartment population PK model with first order absorption and elimination and an allometric scaling effect of body weight on clearance and central volume of distribution. To ensure capturing the initial concentration peak after IV infusion, a two compartment model was tested as well, which resulted in a large, highly significant drop in objective function value (OFV) of 634 points. Allowing the allometric exponent to be estimated freely for clearance did not result in model improvement, but a significant drop was observed when the exponent for central volume of distribution was estimated freely (dOFV = 45.9). Changing from only first order absorption to sequential zero then first order absorption for oral administration was superior to introducing a lag time. The inclusion of lag time is essentially described by a change-point model (no absorption until end of lag time), while sequential zero then first order absorption model accounts for a more gradual absorption leading to an improvement in the description of the absorption phase. Incorporation of a full omega matrix resulted in a further drop in OFV of 72 points. Residual error was modeled using separate proportional error terms for the adult and pediatric population, respectively. No formal covariate search was conducted, but the effect of enzyme-inducing AEDs on LCM clearance in children with epilepsy was kept from the previous pediatric population PK model (Winkler et al., 2015). Final PK parameters are shown in Table 1.

Model diagnostics demonstrated adequate goodness of fit, bootstrapping indicated a close correspondence between NONMEM-

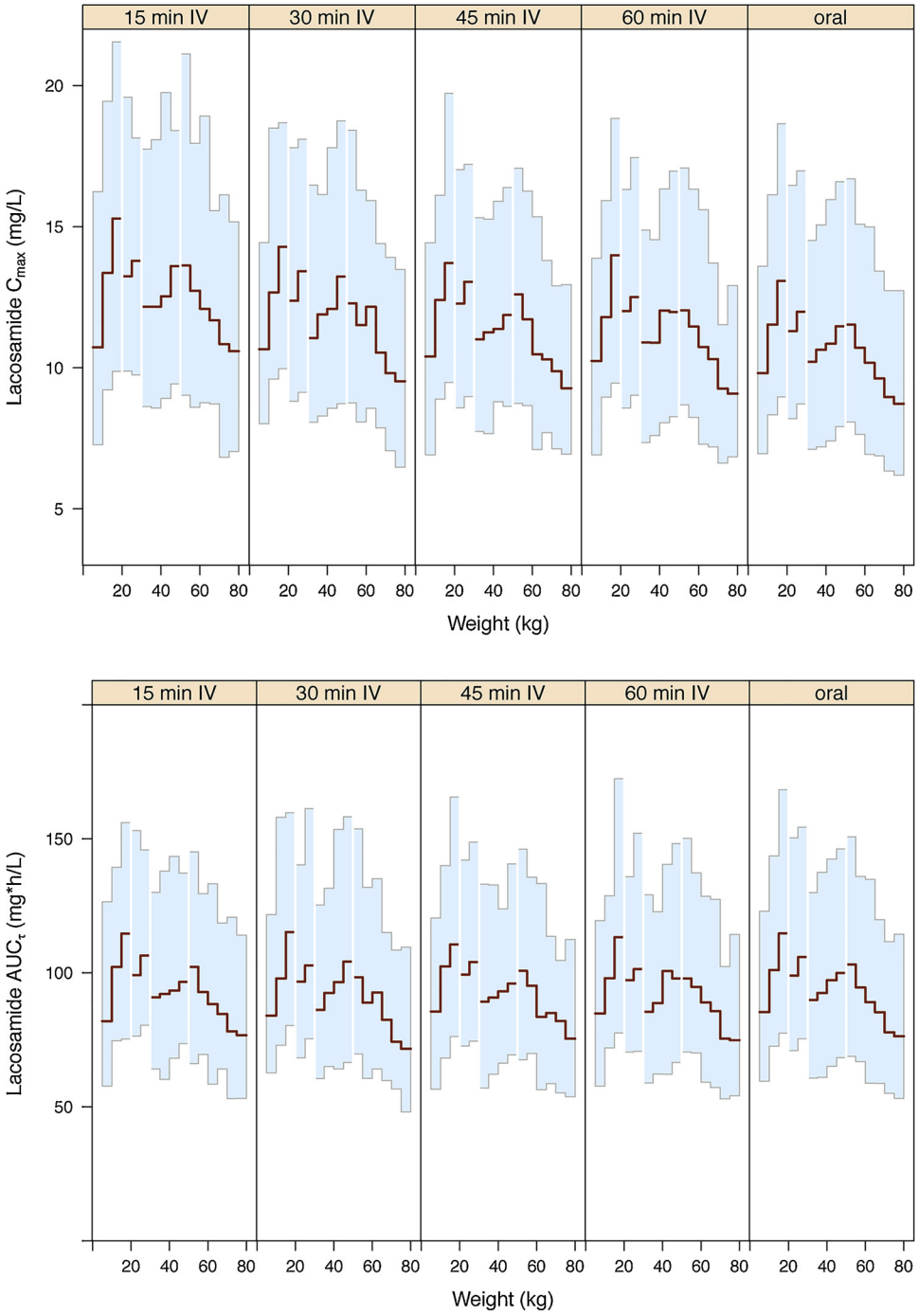

Fig. 1. Predicted steady-state median (5^{th}–95^{th} percentiles) LCM C_{max} and AUCτ across body weight following IV and PO administration as adjunctive therapy (without inducer AEDs).

Footnote

Weight < 20 kg: 12 mg/kg/day; 20 to < 30 kg: 10 mg/kg/day; 30 to < 50 kg: 8 mg/kg/day; ≥50 kg: 400 mg/day. The solid red line shows the median, and the blue area shows the 5^{th}–95^{th} percentiles of 100 simulated children per 5 kg weight band. AEDs = antiepileptic drugs; AUCτ = area under the plasma curve over a dosing interval; C_{max} = peak plasma concentration; IV = intravenous.

estimated precision and bootstrapped results, and visual predictive checks demonstrated that the model was capable of simulating the original data.

Different pediatric dosing adaptations were simulated with the aim of proposing IV dosing regimens in this patient population. Steady-state peak plasma concentration (C_{max}) and area-under-the-plasma curve (AUCτ) after twice daily IV infusions in children with epilepsy that were dosed in mg/kg were predicted to increase with increasing body weight up to the maximum body weight in that dosing group; on the other hand, as expected, a progressive concentration decrease was seen with increasing body weight when a fixed dose was used for body weights ≥50 kg. This is illustrated in Fig. 1 in the adjunctive setting, without enzyme-inducing AEDs. The same pattern was obtained in presence of inducers, or in monotherapy, but with slightly modified C_{max} and AUCτ values (UCB, data on file). Median steady-state C_{max} at the end of a 15-min IV infusion were predicted to be 9–21% higher compared with median C_{max} values after oral administration across the body weight range of 5–75 kg; this decreased to 2–10% after a 60-min IV infusion

compared with oral administration. However, values of AUCτ were fairly similar between oral administration and IV infusion and independent of infusion duration.

4. Discussion

A population PK model after IV infusion and oral administration was developed for LCM in a combined dataset of 43 healthy adults and 79 children with epilepsy. The two-compartment model adequately described the plasma concentration of LCM as a function of body weight and concomitant inducer AEDs.

Different pediatric dosing adaptations were simulated with the aim of proposing IV dosing regimens in this patient population. Using the dosing scheme per body weight band as recommended for oral administration, IV infusion durations of 15–60 min were predicted to yield similar peak (C_{max}) and average ($C_{av} = AUC\tau/12$) exposures, not differing substantially from those after oral dosing. Median steady state C_{max} at the end of a 15-min IV infusion were predicted to be 9–21% higher compared to values after PO administration across the simulated dose range; this decreased to 2–10% after a 60-min IV infusion compared to PO administration. The predicted steady state C_{max} at the end of a 15-min IV infusion were considered to be the worst-case scenario in terms of possible exposure in order to best ensure that a safe regimen will be used. These results indicate that the known efficacy and safety characteristics (including cardiovascular), should not be altered by switching from oral dosing to IV infusion in children, like in adults. The model-based PK predictions suggested that there is no need to adapt the recommendations regarding IV infusion durations in children using weight-based dosing aiming to reach exposures in the same range as in adults.

Although this analysis has reached its aims, there were some limitations. First, pediatric data were mostly sparse and only few subjects provided serial plasma samples compared to the adult population. Secondly, developmental changes in kidney function and expression of metabolizing enzymes were not included in the model due to the limited data in younger age; however, they were indirectly taken into account with the dosing adaptation by both weight and age. And thirdly, a formal covariate search has not been conducted, but from a previous analysis based on the same pediatric data co-administration of inducer AEDs was associated with a modification in clearance and was therefore included.

Disclosure of conflicts of interest

JW and RS were employed by SGS Exprimo when the study was performed; they declare no conflict of interest. AS is employed by UCB Pharma and has received stock options.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Acknowledgments

The study, data, modeling analyses, interpretation and reporting were funded by UCB Pharma.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2018.10.011.

References

Cawello, W., Bonn, R., Boekens, H., 2012. Bioequivalence of intravenous and oral formulations of the antiepileptic drug lacosamide. Pharmacology 90, 40–46.

Cawello, W., Stockis, A., Andreas, J.O., Dimova, S., 2014. Advances in epilepsy treatment: lacosamide pharmacokinetic profile. Ann. N. Y. Acad. Sci. 1329, 18–32.

Ferreira, J.A., Daniels, T., Dilley, D., Dimova, S., Rice, K., Byrnes, W., 2015. Safety and tolerability of lacosamide as adjunctive therapy in children with partial-onset seizures. Eur. J. Paediatr. Neurol. 19 (Suppl. 1), s56–s57.

UCB Pharma, 2018a. Vimpat® (lacosamide Tablets, Injection, Oral Solution) [U.S. Prescribing Information]. Smyrna: UCB, Inc. (Accessed 24 April 2018). https://www.vimpat.com/vimpat-prescribing-information.pdf.

UCB Pharma, 2018b. Vimpat® (lacosamide) EMA Summary of Product Characteristics. (Accessed 24 April 2018). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000863/WC500050338.pdf.

Winkler, J., Schoemaker, R., Stockis, A., 2015. Lacosamide population pharmacokinetics in children from 6 months to 17 years of age. Epilepsia 56 (Suppl. 1), 177.