Title: Model-informed precision dosing of levetiracetam in pediatrics population

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What is already known about this subject

- The recommended doses of levetiracetam are based in the plasma concentration carried out in healthy adult subjects
- Physiologically-based pharmacokinetic modeling (PBPK) is the approach widely applied for doses extrapolations for special populations.
- Currently, levetiracetam has been widely used for the pediatric population in an off-label mode for children under 6 years of age.

What this study adds

- This is the first model to assess the suitability and safety of doses of levetiracetam in the pediatric population using PBPK modeling and present an easy handle model to guide clinicians to decide the first dose to pediatrics.

Abstract

Aims: Assessing the suitability and safety of doses of levetiracetam in pediatrics using physiologic-based pharmacokinetic (PBPK) modeling.
Methods: A PBPK model of levetiracetam was developed and validated for healthy adults and scaled for children (0.5 to 12 years old). Prediction of levetiracetam exposure at steady-state, were carried out for different therapeutic regimens to achieve the target of Cmax values within the therapeutic range of 5 to 46 μg ml^{-1}. Then, a multivariate linear regression analysis (MLR) was applied to correlate the simulated data with covariates: dose, therapeutic regimen, sex, age and body weight (BW), to describe the best model prediction for the initial dosing in pediatrics.
Results: The results indicated the suitability of the PBPK model for adults and pediatrics. For children aged 0.5 to 6 y.o. the dose range capable of reaching the pharmacokinetic target is between 10 and 100 mg kg^{-1} day^{-1}, for 7 to 9 y.o. doses between 20 and 90 mg kg^{-1} day^{-1}, and for 10 to 12 y.o. doses between 20 to 80 mg kg^{-1} day^{-1}. Further, the MLR related Cmax to dose, therapeutic regimen, and BW.
Conclusions: For 3 daily administrations, it is suggested that maximum daily doses of 80 mg kg^{-1} could be used for ages between 0.5 and 6 y.o. and 100 mg kg^{-1} for ages above 7 years old, since they weigh below 50 kg. The PBPK model lumped to MLR could be very supportive for clinical decisions to safety and effectiveness of prescription of levetiracetam along the titration phase.

Keywords: Pharmacometrics, multivariate linear regression, PBPK lumped MLR.

1. INTRODUCTION

Epilepsy is a chronic neurological disease that affects over 50 million peoples of all ages[1,2], with the highest incidence being in the first years of life and in the elderly[3,4]. The treatment with antiepileptic drugs (AEDs) must consider not only the spectrum of efficacy and adverse effect profile of the different medications, but also the disposition of the drugs and their implications in the pharmacokinetics changes related to the different[5]. The physiological changes in neonates and children like the body composition, and the immaturity of the metabolism may affect the drug pharmacokinetic profile which reflects on the Clearance and elimination half-life[6].

The levetiracetam (LEV) is one the most common drugs used to treat epilepsy, mainly for focal seizures as add-on therapy for children older than 4 years old, but it has also been prescribed for children older than 1 month in Europe. Levetiracetam is not recommended for neonates[7].

Franco et al., showed that in Europe 43% of the prescriptions LEV are off label in children[8]. A wide range of dosing is recommended for children older than 6 years old varying from 1000-3000 mg day^{-1} in order to maintain the therapeutic target of 5-46 mg mL^{-1} in plasma to adults[9–11] and 20-30µg mL^{-1} in children[12].

The LEV is well absorbed by gastrointestinal tract (GI) with a fraction absorbed of almost 100%[13]. The plasma protein binding is about 10% in albumin, and the volume of distribution is 0.6 L kg^{-1}. Mainly excreted unchanged in urine (66%), the LEV clearance is affected by renal function, pediatric patients aged 6-12 years old have 30-40% higher clearance than adults[14]. Thirty four percent of the drug is metabolized by esterase and excreted as a non-active metabolite[13].

The majority of the LEV pharmacokinetics data available comes from studies carried out in healthy adults. In spite of several children presenting epilepsy, the scarce LEV data in children may categorize the treatment for this disease in children as an “orphan drug”, where drug safety and efficacy is not completely established[16]. LEV adverse events are correlated with behavioral disturbance especially in pediatrics population, There is not enough evidence that this condition is dose related, but it can be can be associated if rate of titration[17,18].

In this context, the Model-Informed Precision Dosing (MIPD) can help define safety and effectiveness of doses for clinical protocols based on Modeling and Simulation (M&S)[19].

The MIPD approach is already implemented at hospitals to support clinical decisions. Recently Frymoyer et al. 2020 demonstrated the successful implantation of MIPD, to support clinical decisions regarding the use of vancomycin for pediatric population[20].

The MIPD can be built by different approaches. One of them is the Physiologically based Pharmacokinetic modeling (PBPK) analysis[21,22] to build models and simulate clinical conditions. Then, the goal of this study is to explore the safety and the effectiveness dose regimen for the pediatric population for off-label dose prescription of levetiracetam by PBPK modeling and simulation.

2. METHODOLOGY

2.1 PHYSIOLOGICAL-BASED PHARMACOKINETIC MODEL DEVELOPMENT

For the development of the LEV PBPK model, the GastroPlus software version 9.8 (SimulationsPlus, Lancaster, CA) was used. The drug-dependent parameters for LEV were based on in vitro experimental data (logP, pka, molecular weight, solubility, fraction unbound, permeability, plasma to blood ratio) from literature[23–26].

The partition coefficients (Kp) were estimated by the Lukacova (Rodgers-Single) method [Table 1].

Insert [Table 1]

Published data of pharmacokinetic information for LEV after intravenous and oral administration, single or multiple doses were found in scientific literature. To guide the building model, only studies with known demographic information such as age, gender, height, weight, renal function, dosing information, and plasma concentrations were selected, and they are listed in [Table 2]. In these publications data for adults and pediatric populations were found.

The observed plasma profile was digitally extracted using WebPlotDigitizer 4.2[31] for the purpose of overlaying these data onto the summary model-predicted concentration-time profiles. For publication that did not provide summary exposure parameters, the AUC and Cmax were determined from the averaged profiles using non compartmental analysis.

The PBPK was performed with the software GastroPlus 9.8.0002, using the PBPK platform for full PBPK model. The concentration-time profiles and exposure parameters, AUC and Cmax, were generated from the PBPK simulations.

The full PBPK prediction strategy followed the three-stage method previously reported by Jones et al. 2011 and Martins et al. 2020[32,33], with modifications. The first step was the development and performance verification of the model using adult healthy volunteers (HV) data after single and multiple intravenous administration. For the next step, the model built was used for simulations of plasma exposition after oral administration for single or multiple doses. Finally, the last step was the extrapolation of the model to the pediatric population aged between 0.5 and 12 years old.

2.2 AGE-DEPENDENT SCALING OF PBPK MODEL PARAMETERS

Protein binding: The Fup pediatric scaling was based on the previously published[34] equation 1 and assumes that the input experimental percent unbound in plasma is representative of nonspecific drug-protein binding in adult plasma:

$$Fup_{ped}\frac{1}{1+\frac{P_{ped}}{P_{adult}}.\frac{(1-Fup_{adult})}{Fup_{adult}}} \quad (1)$$

Clearance: The total clearance was calculated as the sum of its individual clearance pathways. For LEV, the clearance in children was calculated as the sum of scaled non-renal clearance (lamped as hepatic) and renal clearances using a physiologically based approach equation 2 and 3.

$$CL_{hepatic(child)}=\frac{Q_{h(child)}\cdot f_{u,p(child)}\cdot CL_{\int(child)total\,liver}}{Q_{h(child)}+\left(f_{u,p(child)}\cdot CL_{\int(child)total\,liver}\right)/B/P_{(child)}} \quad (2)$$

To scale adult renal clearance values toward pediatric patients, the estimated GFR of the child, as determined using Hayton's algorithm, was used in conjunction with the following equation proposed by Edginton et al. (2006)[35].

$$CL_{GFR(child)}=\frac{GFR_{(child)}}{GFR_{(adult)}}.\frac{f_{u,p(child)}}{f_{u,p(adult)}}.CL_{GFR(adult)} \quad (3)$$

where CL_{GFR} (child) is the child's clearance due to glomerular filtration, GFR (child) GFR (child) is the estimated GFR of the child, GFR (adult) GFR (adult) is the GFR in adults

(assumed to be 110 mL min^{-1}), and CL_{GFR} (adult) CL_{GFR} (adult) the clearance due to glomerular filtration in adults.

Anatomy/Physiology: The age dependence of body weight, height, organ weights, and blood flows represent those values currently used as default values in GastroPlus®.

2.3 MODEL PERFORMANCE VERIFICATION

The exposure parameters predicted from the PBPK model were qualified against available pharmacokinetic data for LEV. The performance verification consisted of 100 subjects per simulation, using identical demographical and dosing information from literature, taking into account the dose, route of administration, age, gender proportionality (male/female ratio), ethnicity and body weight [Table 2].

Insert [Table 2]

The suitability of the PBPK model was defined assuming visual checking of the overlapped predicted versus observed data graph of predicted pharmacokinetic profile and observed data, and by the mean fold-error (MFE) [equation 4] for AUC, Cmax obtained.

$$MFE = \frac{PK\ parameter_{\ predicted\ mean}}{PK\ parameter_{\ observed\ mean}} \quad (4)$$

The model was accepted when all predicted PK parameters were within two−fold of the corresponding observed values (MFE 0.5–2.0)[39].

2.4 PEDIATRIC DOSE SCALING IN PEDIATRIC POPULATION

The plasma levels at steady-state conditions were simulated for ages between 0.5 and 12 years old. The ages were stratified in a) 0.5 to 3 years old b) 4 to 6 years old; c) 7 to 9 years old and d) 10 to 12 years old.

The suitability of pediatric doses was evaluated as PK target, the plasma therapeutic window for adults (5 to 46 mg L^{-1})[10,11,40].

Different doses (from 10 to 135 mg kg^{-1}) and administration regimen (twice and three times per day) were simulated in 10 repeated trials with 15 sample sizes for each level of ages for pediatrics. The doses were considered acceptable when Cmax values of LEV were inside the plasma therapeutic window[41]. All graphics presented were plotted in Rstudio software version 1.3.1093, using the ggplot package.

2.5 MULTIVARIATE LINEAR REGRESSION ANALYSIS TO GUIDE THE FIRST DOSE PRESCRIPTION

One trial dataset for each dose, regimen and level of age were randomly selected. Age, weight, Body Surface Area (BSA), Height, daily dose and Cmax at SS were used to build the dataset for BID or TID regimen. The Cmax was the dependent variable, and all other factors were evaluated in the model. The forward inclusion of each factor was performed. The multivariate linear regression analysis was performed to build a model for dose selection for pediatrics. The analysis was run in the Rstudio package tidyverse. All significant variates were included at the model ($p < 0.05$).

The multivariate linear equation has the general model as presented in Equation 5.

$$DV=\beta0+\beta1*x1+\beta2*x2+\beta3*x3+\beta4*x4+\ldots+\beta n*xn+\varepsilon \quad (5)$$

where β represents each coefficient related to each factor x and ε is the standard error of regression.

3. RESULTS

The values of predicted and observed PK parameters of LEV in adults and pediatrics population after IV and oral dose are summarized in [Table 3].

Insert [Table 3]

The MFE values of AUC and Cmax were between 0.57 and 1.32 and were considered adequate for adults and pediatrics data.

Representative summary of model-predicted LEV concentration-time profiles after intravenous and oral administration in adults and pediatrics are shown in Figure 1.

The visual (Figure 1) shows the adult model predictions and the observed data of LEV concentrations in healthy adults after a single dose of 1500 mg IV (a)[27] single oral administration of 3500 mg (b)[13] used for model building. Only two plots used for the validation process are presented as illustrations: the multiple dose administration of 500 mg (c)[36] and the single oral administration 40 mg kg^{-1} (d)[38].

The Goodness-of-fit graphs for Cmax and AUC can be seen in Figure 2.

Insert [Figure 1] and [Figure 2}

Assuming the dose recommendation of LEV to children weighted less than 50 kg is 10 to 30 mg kg^{-1} twice a day, doses 10 to 120 mg kg^{-1} were simulated twice a day (BID) and three times a day (TID).

[Table 4] shows the Cmax values for the pediatrics population between 0.5 to 12 years separated in four levels of ages and dose regimen tested. In this work, the stratified ages were named ages level 1, 2, 3 and 4, respectively.

Insert [Table 4]

The highest doses to achieve the PK target according to level of ages were a) for 0.5 to 3 y.o., 100 mg kg^{-1} day^{-1} b) for 4 to 6 y.o., 100 mg kg^{-1} day^{-1}; c) for 7 to 9 y.o, 90 mg kg^{-1} day^{-1}, and d) for 10 to 12 years old 80 mg kg^{-1} day^{-1}. The Cmax values for each regimen are described in [Table 4]. In Figure 3 the average of maximum concentration (Cmax), the minimum and maximum interval achieved for each dose regimen and group of age are presented.

Insert Figure 3

The simulations showed that for all levels of ages, since they weighed below 50 kg (110 lb), the highest efficient doses to achieve the therapeutic window were about 2.5 times higher than the dose recommended. However, for children weighing above 50 kg, independently of the age, the dose able to achieve PK target is the same as for adults (1000-3000 mg day^{-1}).

The BID or TID regimen have an important impact on safety, reading according to Cmax. For all range of ages, the higher dose able to produce Cmax within the therapeutic regimen is 60 mg kg^{-1} day^{-1}. However, if the TID regimen is assumed, for children aged 0.5 to 6 years, the highest dose that generates Cmax into the therapeutic range was almost twice higher (100 mg kg^{-1} day^{-1}).

When the ages 7 to 12 years old are observed, considering TID, the maximum dose indicated is 80 mg kg^{-1} day^{-1}, lower than observed for younger children.

The multivariate linear regression results are presented in [Table 5]. Only the significant variables were kept in the model for dose adjustment for pediatrics.

Insert [Table 5]

The multivariate linear equation has the general model as presented in Equation 5.

$$DV=\beta0+\beta1*x1+\beta2*x2+\beta3*x3+\beta4*x4+\ldots+\beta n*xn+\varepsilon \quad (5)$$

where β represents each coefficient related to each factor x and ε is the standard error of regression.

Thus, the results show the significant regression values for both regimen and the final model for pediatric dose adjustment is presented as Equation 6.

$$Cmax=(11.155\pm0.783)+(0.485\pm0.005)*Dose+(0.146\pm0.016)*WT-(8.526\pm0.384)*Reg \quad (6)$$

where Cmax is given as mg L^{-1}; dose is given as mg kg^{-1} day^{-1}, WT is the weight in kg, and Reg is the Regimen as 1 for BID and 2 for TID.

4. DISCUSSION

MIPD approach is the newest designation in the Pharmacometrics field and the first papers using this term is from 2017[19,42–44].

This recent term came from the fusion of the concepts and tools of Personalized Medicine (PM), Therapeutic Drug Monitoring (TDM), Modeling and Simulation (M&S) and Statistics.

However, other than finding doses for individuals, the MIPD can be a strong tool to review labeling decisions for different populations. Nowadays, the off-label prescriptions are frequent in clinical offices. For pediatricians, these “off-label practices” are routine for many reasons that will not be discussed in this paper.

For LEV, the tradicional prescription includes children over 6 y.o., but it used to be prescribed for the younger pediatric population as off-label, as previously described.

The PBPK modeling is a pharmacometrics approach that applies ontogeny for populations. Looking through this analytical point of view helps understand better the impact of all stages of biological maturation over the pharmacokinetic response. For that reason, defining bins of ages is an important starting point to predict bias of comprehension.

Officially, the general consideration of the pediatric population includes children with ages from preterm until above 17 years old, and this group is usually stratified in three ranges of ages, building the subpopulations of neonates (0 to 3 months of age), children (4 months to 10 years old) and adolescents (11 to 17 years old)[45,46].

For ethical reasons, for drugs in general, a restricted number of pharmacokinetic clinical data for pediatrics is available. For LEV, this scenario is not different. Three studies with pediatrics were found [14,38,47] and the ranges of ages presented in each publication did not correspond to the classical stratification. For this work, we assumed the age stratifications according to each publication instead of the traditional[46].

The known therapeutic window for LEV is 5 to 46 mg L^{-1} [9–11] as described previously, but other authors have raised a different range for children. Iwasaki et al. (2015) led a study in 24 Japanese children (age from 0.7 to 16.7 years old) with focal seizures. In this study, the researchers measured LEV blood concentrations, 1-2 hour after administration [12] and considered these highest concentrations as Cmax. They reached what they called the optimal therapeutic range, with no adverse effects, when Cmax was between 20-30 μg mL^{-1} [12].

Considering that the goal of this work was to reproduce as close as possible, the actual clinical conditions, the therapeutic window assumed was the most applied by the practical scenario: 5 – 46 mg L^{-1} [9–11].

Apart from the therapeutic window, the PK target for TDM needs to be correlated to the effects. In this way, to evaluate the evidence of efficacy and safety of dose prescription in children, the Cmax parameter was considered as a PK target. This decision was based on a previous publication where the researchers could relate only Cmax to a biomarker of activity (the cytokine IL1-beta), but not Cth [41]. This biomarker chosen by the researchers is plenty justifiable[48,49]. As discussed above, Iwasaki et al. (2015) considered only Cmax as the PK target, as well.

The PBPK models built for adults have been extrapolated to define pediatric dosage for many classes of drugs. These extrapolations are being used to other goals, such as evaluating drug-drug interaction, the food effects over PK profile, and more recently, the PBPK in the MIPD is able to review dosing regimen for populations[19].

LEV is considered one of the safest antiepileptic drugs and the glomerular filtration as a prior elimination process is one of explanations for that. For LEV, 66% of total Clearance (CLtot) is known to be through glomerular filtration and 34% by esterase metabolism[13]. However, not enough information about metabolic processes is available. There is suggestion about serum esterase [50] or esterase in liver [51,52] however which enzyme is properly involved in

the 34% of metabolic process is not clear. Because of this, in this work we assumed the 34% as non-renal Clearance (CL_{NR}), without metabolism specification and 66% as glomerular filtration.

These assumptions for elimination processes showed up efficiently to the LEV PBPK model for adults and pediatrics. The extrapolation from adults to pediatrics was based, mainly, on glomerular filtration rate (GFR) and unbound plasma protein fraction (Fup). This physiological rationale is justifiable because the renal function is dependent on renal morphogenesis, functional renal maturation, and hemodynamic[53].

The PBPK model assumed higher values for GFR in pediatrics to adults. The GFR levels reported for adults are around 120 mL^{-1} min^{-1} $1.73m^{-2}$. For this model, the GFR adjusted and assumed for adults was lower than this. The known partial subsequent tubular reabsorption process[13,54] can explain the necessary decrease on GFR to build the model. The GFR is dependent on blood flow and organ sizes[53,55,56]. In this way, assuming physiological scaling of these factors can help evaluate doses in different scenarios and ages more accurately. The same proportional decrease was assumed for GFR for each pediatric bin of ages and these procedures could represent the elimination properly for all ages, as discussed above.

The results showed that the variation on pharmacokinetic profile for all ages tested, could be explained by the physiological variability for children below 6 y.o. until 0.5 y.o. after single administrations. The simulated PK profiles could be overlapped to the observed data [14,30,38] indicating suitability of the PBPK model for adults and pediatrics until 0.5 y.o.

After the pediatric PBPK model has been qualified, it was used to explore the evidence for safety on prescription of LEV for lower ages and higher doses than the recommended.

As discussed previously, the Cmax between the therapeutic window was assumed as the PK target for this work. However, to be more assertive the Cmax at the steady state condition was assumed to evaluate the evidence of efficacy and safety of dose prescription in children.

The simulated data for distinct doses (from 10 to 135 mg kg^{-1} day^{-1}) and regimens (BID and TID) showed that the Cmax could achieve the traditional therapeutic window (5-46 mg L^{-1}) from 10 mg kg^{-1} dose to 80 mg kg $^{-1}$ for BID for all ages tested. For TID regimen, the lower dose able to achieve the target was 20 mg kg $^{-1}$, however, this regimen allows the increasing the maximum daily dose (DD) to 100 mg to younger children (0.5-6 y.o.), by one more partition of the daily dose (see Figure 3 for a better visual comprehension).

These higher doses of 90 to 120 mg kg^{-1} for pediatric patients were already reported in the past by clinical studies after oral and intravenous administrations. Patients with mean age of 2 y.o had received 90 to 120 mg kg^{-1} day^{-1} after intravenous administration[57], and older pediatrics (mean age 11 y.o) had doses between 90 to 120 mg kg^{-1} day^{-1} after oral administration as a monotherapy or as adjuvant[58]. For both situations, the effectiveness in reducing the frequency of seizures crisis and safety was demonstrated.

Some research defended the age as a key factor for dose definition for pediatric, where it should be higher than adults [14] based on the ontogeny of renal clearance which is 30-40% higher in pediatrics than adults[13,14,38,47].

Considering the Monte Carlo simulations of each trial performed for children until 12 years old, most of these virtual children weighed lower than 50 kg. For these virtual pediatric patients, the weight defines the variability in the amount of the dose, even for patients with the same ages. However, for children above 50 kg, the relationship between doses and Cmax was equal to adults.

Considering that the clinical dose adjustment starts with titration of the patient, until now, no strong evidence of safety supported pediatricians to increase dose further than 30 mg kg^{-1}. Thus, these simulations could suggest that, if doses until 30 mg kg^{-1} do not bring an efficient response over seizures control, higher doses could be tried before changing the drug or including a second one, keeping the patient in a monotherapy.

It is important to highlight two limitation points of this work for a fully extrapolation of the model. Firstly, the M&S was developed only for the monotherapy condition with LEV and; secondly, for patients with no comorbidities. As described, many therapies require more drugs and an interaction effect between LEV and other antiepileptics or other classes of drugs cannot be discarded [59,60]. Furthermore, the effect of the disease progression and/or the comorbidities over the pharmacokinetic profile.

In the clinical offices, doctors need to handle the signs and symptoms of their patients. The necessity of increasing doses above the traditional recommendation or, prescribing drugs not indicated for that age or clinical condition, is recurrent. Looking to support and give confidence to physicians, this work suggests that it is safe to prescribe doses from 10 to 90 mg kg^{-1} for children from 0.5 years old to 6, and until 120 mg kg^{-1} for children older than 6 y.o. All pharmacometrics evidence suggested safety for prescription of LEV for ages above the labeling.

Besides the population studies presented here, for the usual clinical environment it is desirable that individual dose adjustment should be easy, practical, and not consuming of time

or money. The initial proposition of doses could be more rational, based on probabilities to achieve the defined Cmax for each case.

Recently, Standing (2017) wrote that "pharmacometrics encompasses the analysis of PK and PD data, and then uses resulting models to make inferences (often using simulation) on optimum dosing for clinical trials or practice". Therefore, thinking in a simpler way for the clinical practice, the PBPK simulation results were reviewed under the lens of another statistical method, the multivariate linear regression (MLR). It is a traditional statistical approach to correlate multiple factors to a specific response[61].

To explore statistical correlations, simulated characteristics of patients in different trials were raised and used to correlate Cmax to dose as presented in the Methodology section. Height, BSA, gender and age were not significant to describe the dependent variable Cmax. However, weight, dose, and dose regimen (Reg) together determine Cmax values. The regression was able to explain around 93% of data, indicating that the individual dose adjustment equation could be a promising tool to guide initial prescriptions for children.

The equation (6) could be used as an initial estimator of doses for children from 0.5 years old until older ages as long as they weigh less than 50 kg, for patients in monotherapy with LEV.

The ANOVA results show, numerically, how important the regimen factor is to define Cmax. The TID regimen allows doctors to increase the amount administered. Lower fluctuation in plasma levels make it possible to increase dose without having achieved the desirable maximum plasma concentration. Weight is the most important individual factor to describe the dose-Cmax relationship as well.

All results discussed here showed the MIPD as a strong tool to be used for decision-making for pharmaceutical companies and surveillance agencies to the bedside professionals. The PBPK lumped MLR was able to propose an easy model to be used by physicians. However, the proof-of-concept needs to be done yet. Then, the MLR model should be provoked by new and independent pediatric clinical data.

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