Personalised pharmacotherapy in paediatric epilepsy : the path to rational drug and dose selection

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CHAPTER 8

EXPOSURE-RESPONSE RELATIONSHIP AND DOSE RATIONALE FOR LAMOTRIGINE IN CHILDREN AGED 1-24 MONTHS

Exposure-response relationship and dose rationale for lamotrigine in children aged 1-24 months

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SUMMARY

Objective: The anti-epileptic drug (AED) lamotrigine (LMT) is approved for treatment of partial-onset type seizures in adults and adolescents. Given the known differences in pharmacokinetics in this age group, we aim to investigate the dose rationale for lamotrigine using a model-based approach that has been developed for older patients. **Methods:** Data of children aged 1-24 months with partial type seizures receiving LMT as adjuvant therapy were retrieved from the clinical database of GlaxoSmithKline. A PKPD Poisson model with Markovian features was used to describe seizure counts over time, along with the drug effect. The dose rationale was evaluated taking into account differences in pharmacokinetics and the PKPD model parameter estimates. The analysis was complemented by the simulation of a clinical trial in which paediatric patients are treated with doses that yield exposures comparable to the efficacious range observed in the age range > 24 months. **Results:** The use of a drug-disease model provided insight into the exposure-response relationship of lamotrigine in infants and toddlers. Model parameter estimates were comparable to those in adults with partial seizures. The main difference was in the placebo effect, which was significantly larger. Maximum efficacy was enough to suppress disease activity, while potency (EC_{50}) was slightly higher than in adults. Clinical trial simulations showed that statistically significant differences can be detected and efficacy demonstrated when differences in pharmacokinetics and placebo effect are taken into account. **Conclusions:** The use of a drug-disease model allows for the characterisation of exposure-response relationship of lamotrigine in children younger than 2 years of age. It appears that lamotrigine is efficacious in patients younger than 2 years with partial onset seizure and that efficacy can be extrapolated from adults and older paediatric patients

1. Introduction

Roughly 68 million people worldwide suffer from epilepsy, with up to 25% of those patients belonging to the paediatric subpopulation [1,2]. Poor and rural areas contribute to a disproportionate degree to that number, leading to a need for anti-epileptic drugs (AEDs) that are efficacious and safe for children, yet affordable. Most of the popular AEDs have been thoroughly investigated in adults, but due to ethical and practical constraints, little is known about their pharmacokinetics (PK) and pharmacodynamics (PD) in very young children[3,4]. Given the lack of data, many AEDs have not been approved for use in subset of the paediatric population, but are nevertheless used off-label[5] by clinicians. Consequently, many paediatric patients receive unproven medical treatment daily, possibly with the inappropriate drug and dosing regimen, possibly exposing patients unnecessarily drug levels and long titration times [6,7].

Lamotrigine (LMT)[8] an AED with predictable PK and a favourable efficacy and safety profile in adults and adolescents [9,10]. Recently, we have described the development of a population-wide pharmacokinetic model for LMT in patients aged 0.2 – 91 years of age. The analysis showed that body weight-adjusted clearance in the younger (1-24 months) population is higher compared to that in older patients. In fact, a maturation function is required to account for the differences observed in this age group [11]. This model was subsequently used as basis for another investigation, in which we have attempted to characterise the exposure-response relationship of lamotrigine in adults with partial-onset (PO) and primary generalised tonic-clonic (PGTC) seizures using a Poisson model with Markovian features [12]. LMT has been approved for the treatment of partial- and primary generalized seizures in patients with epilepsy aged 2 years and older, but failed to show adequate efficacy compared to placebo in a small sample of subjects 1-24 months old (N=38) [13]. A possible cause of this lack of efficacy may have been the lower exposure that was reached in this population due to the higher drug clearance relative to body-weight. However, in paediatric epilepsy, epileptologists suggest that differences in the epilepsy in adults and young children are the likely cause of lack of efficacy. Here we attempt to explore whether the underlying exposure-

response relationship of lamotrigine truly differs between populations and most importantly whether failure in detecting efficacy can be assigned to inaccurate dose selection and sample size. While a new trial may be required to ultimately prove this hypothesis, we show how these questions can be addressed using clinical trial simulations (CTS) [14]. A secondary objective is to establish the feasibility of bridging concepts in paediatric epilepsy.

2. Methods

2.1 Subjects & original study design

Data from a clinical efficacy and safety study of LMT in children was used (clinicaltrials.gov ID NCT00043875). Included were male and female subjects between the age of 1-24 months at study entry, with a confident diagnosis of epilepsy and a history of at least four reliably detectable recurrent partial seizures per month. Seizures were required to be uncontrolled by at least one other AED with plasma concentrations within the acceptable therapeutic ranges. Subjects were included if they had a diagnosis of severe, progressive myoclonus, had seizures not related to epilepsy or as the result of drug withdrawal. Subjects were not allowed to suffer from clinically relevant chronic conditions which may affect the LMT PK.

Subjects were required to submit at least two weeks of historical baseline daily seizure counts at inclusion. Once included, they were up-titrated with LMT to a dose of 5.1 mg/kg/d (when combined with VPA or non-enzyme inducing AEDs) or 15.6 mg/kg/d (given in combination with enzyme inducing AEDs). After titration, patients were further optimised according to clinical efficacy and safety according to the treating physician. These titration and optimisation phases occurred during the open-label phase (OLP). At the end of the OLP, those patients with a reduction in seizure frequency of at least 40% compared to baseline were allowed to continue to the double blind phase (DBP), with a maximum of 38 subjects. In the DBP, subjects were randomised in a 1:1 ratio to either LMT continuation or

LMT down-titration and subsequent conversion to placebo. During the DBP, escape criteria were used to determine treatment failure. These criteria were at least 50% increase in monthly seizure frequency, having double the amount of consecutive 2-day seizure counts compared to the optimisation phase, onset of a new and more severe seizure type, clinically significant worsening of non-partial seizures, the need to therapeutically intervene to control seizures, or status epilepticus. An overview of the trial phases can be found in **Figure 1**.

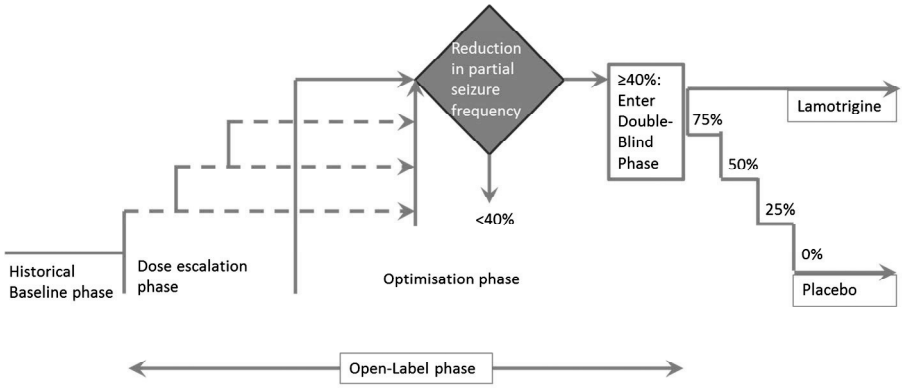

Figure 1. Schematic overview of the trial phases involved in the original study.

An overview of the demographics is shown in **Table 1**. The previously developed PK model [11] in combination with the available concentration and covariate data was used to predict individual values of peak, mean and trough concentrations (Cmax, Cavg, and Cmin respectively) for every day of the study duration in the dataset. Data manipulation, and statistical and graphical analysis were performed using R v3.1.1 [15]. Model building was performed using an environment consisting of NONMEM v7.3[16], Piraña v2.9.0 [17], and PsN v4.2.0 [18].

Table 1. Subject demographics for the data used in this study. Numbers of subjects receiving co-medications are listed, with the dose range given in parentheses.

Variable	Mean (SD)
Number of subjects	170
Weight (kg)	11 (2.2)
Age (y)	1.3 (0.4)
Seizure freq (day^{-1})	5.576 (10.8)
Comedications:	N (dose range)
Carbamazepine	56 (1-800)
Clobazam	10 (1-15)
Clonazepam	27 (0.05-25)
Diazepam	6 (0.9-30)
Gabapentin	1 (400-400)
Levetiracetam	2 (62.5-500)
Lorazepam	3 (0.20-0.75)
Oxcarbazepine	5 (90-540)
Phenobarbital	66 (8-300)
Primidone	2 (62-125)
Phenytoin	16 (14-300)
Topiramate	33 (12.5-400)
Valproic acid	18 (150-600)
Zonisamide	5 (50-200)

2.2 Pharmacodynamic analysis

The seizure count data was described with a Poisson distribution, consisting of a single parameter lambda (λ), which describes both the number and variance of the distribution of events (seizures per day). If k is the number of events, the probability of observing k is given by equation 1. Given the difficulties of estimating factorials, k! was approximated using the Stirling formula (equation 2). Differences in lambda were identified between baseline, placebo effect and treatment effect. Separate lambdas were estimated for the case when seizures or no seizures occurred on the previous day, which is the Markov element in this model. Over- or under-dispersion were taken into account by estimating an overdispersion factor. In the current application of the model, stochastic differential equations were not included. A more technical discussion of the model may be found elsewhere [12,19].

$$P(x = k) = \frac{\lambda^k}{k!} * e^{-\lambda} \quad (1)$$

$$k! \sim \sqrt{(2\pi k)} * \left(\frac{k}{e}\right)^k \quad (2)$$

Baseline seizure rate was separated from placebo and treatment effect, with treatment effect either as a constant factor or resulting from LMT exposure as measured by average, peak or trough daily concentration. After the introduction of each covariate, the change in objective function value (OFV) was determined, with a decrease of 3.84 points or more considered an improvement with $p<0.05$. Followed by this forward inclusion, backwards exclusion was applied to determine if the data was as well described after elimination of the model element. PD models were evaluated using observed (DV) versus predicted seizure amounts per day (IPRED), cumulative observed versus individually predicted seizures per day, difference (residual) between cumulative observed and individually predicted seizures per day over time, and predicted versus observed overdispersion.

2.3 Clinical trial simulations

To determine the impact of the choice of number of subjects on the ability to estimate statistically significant difference between lamotrigine and placebo trial arms, seven scenarios were created, ranging in number of subjects from 40 to 500. Parameters for baseline disease severity, OVDP, EC_{50} and Emax were sampled from distributions estimated from the original thirty-eight subjects included in the original trial. Exposure to lamotrigine was varied from levels as those found in the original trial to levels adjusted for the increased clearance in the population at levels of 25%, 50% and 75%. For each of the scenarios, the last four weeks of the optimization phase and four weeks of double blind phase were simulated. Statistical significance of differences in changes in seizure frequency between optimisation and double blind phase were estimated using a one-sided mid-p test.

3. Results

3.1 Clinical trial results

Steady-state concentrations as predicted by the PK model were relatively low (mean: 4.05, sd: 7.89, range: 0.23-10.7 mg/L) compared to the therapeutic range as defined for adults (4-12 mg/L). In previous studies in adults with PO-type seizures, average steady-state concentrations were around 6 mg/L. The primary endpoint, i.e. reaching escape criteria, occurred in 58% of LMT-treated patients and 84% PBO-treated patients, at a p-value of 0.07 this was not found statistically significant. Secondary endpoints such as time to escape also showed differences between LMT and PBO that approached statistical significance. Large variability was observed in seizure frequency both between and within individuals. The use of LMT did not result in statistically significant increases in side-effects compared to PBO. The overall lack of statistical significance in clinical endpoints based on the responder-enriched study design pointed to an underpowered study design.

3.2 Pharmacodynamic Model

A pharmacodynamic model was built based on a Poisson distribution with an overdispersion factor and Markovian features, as described previously by others [19]. Baseline lambda was dependent on the previous day and was modified by either a placebo or treatment effect. Treatment effect was dependent on average daily concentrations as predicted by the PK model. Estimated parameter values can be found in **Table 2**. The PD model was able to describe the data reasonably well with only moderate over- or under predictions of seizure counts per day and it followed the general trend in seizure counts over time well (**Figure 2**). Overdispersion was highly similar between observed and predicted seizures. While many variants of the model and many covariates were investigated, no improvements could be made on the base model.

Table 2. Parameter values of the final model, all parameters but EC_{50} are on the log scale.

Parameters	Parameter value (%RSE)	Parameter value in adults	Variance as Ω^2 [%RSE] (Shrinkage %)
Lambda (PDV>0)	-0.879 (6%)	-0.992	8 [26.6%] (28.4%)
Lamdba (PDV=0)	0.181 (93.9%)	-1.22	3.53 [16.3%] (3.4%)
OVDP	-2.45 (10%)	-1.26	9.31 [24.3%] (15.3%)
EPB	-1.82 (28%)	-0.247	1.41 [56.2%] (71%)
Emax	-5.11 (5.1%)	-4.70	63 [26.8%] (26.5%)
EC_{50}	6.17 (11.3%)†	13.06†	12.3 [21.2%] (18.6%)

OVDP: overdispersion factor; EPB: placebo effect; Emax: maximum LMT effect; EC_{50}: average daily concentration of LMT at which 50% of the maximum effect is reached, on normal scale.

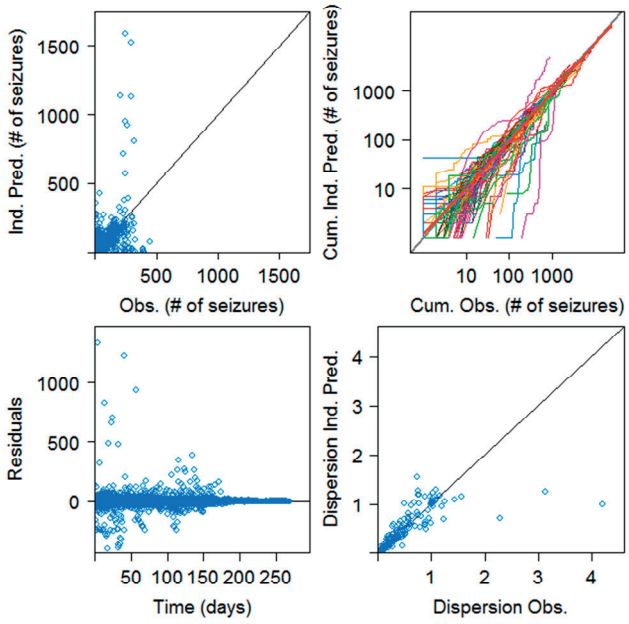

Figure 2. Goodness-of-fit for the final model. Top left panel: Individual observed versus predicted seizure counts. Top right panel: cumulative individual observed versus predicted seizure counts. Bottom left panel: residuals () of seizure counts. Bottom right panel: observed versus predicted dispersion.

3.3 Clinical trial simulations

Clinical trial simulations were performed based on several levels of subject inclusion. The model predicted subjects reaching escape criteria based on the actual trial data well. Simulations showed that increasing numbers of subjects would increase the power of the trial and reduce the p-value accordingly. A minimum of 200 subjects was required to achieve a p value of 0.05 or less at a power of 80% in simulated trials (**Figure 3**).

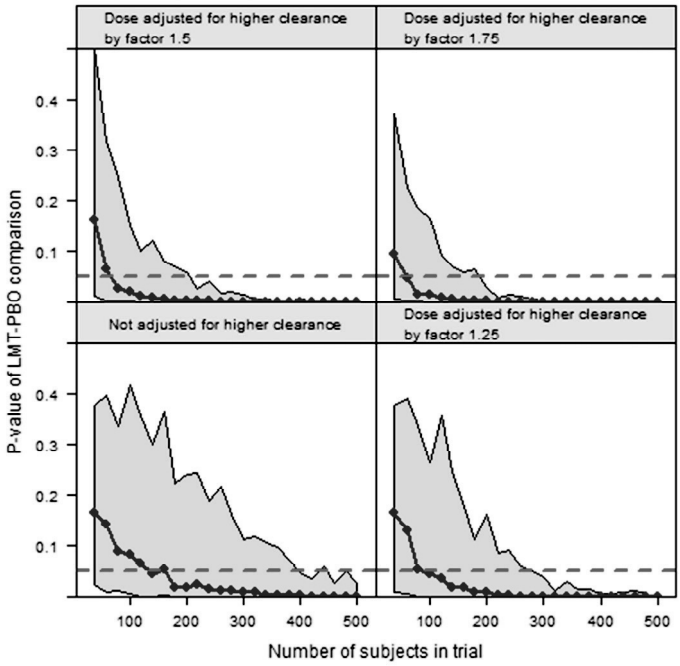

Figure 3. Median p-values (blue lines & dots), depending on the number of subjects in the virtual clinical trial and the level of exposure compared to the original trial. The shaded area represents the 80% prediction interval for each scenario, based on 100 simulated runs. At the number of subjects where the shaded area dips below the red dotted line, the trial design has reached a predicted p-value of below 0.05 at a power of 80%. LMT: lamotrigine; PBO: placebo

4. Discussion

In this work we set out to determine the exposure-response relationship of lamotrigine in children aged 1-24 months and establish the dose rationale for prospective clinical trials using modelling and simulations. Thanks to the availability of historical data, including studies in which seizure counts were collected in individual patients, we have shown that treatment response to LMT can be characterised by the same Poisson model with Markovian features used for adults and older paediatric patients. Most importantly, model parameter estimates describing disease specific properties were found to be of the same order of magnitude across age groups. The actual difference in this population is the placebo effect, which is significantly larger in young children. Based on clinical trial simulations, it appears that statistically significant differences can be detected and efficacy demonstrated if exposure is adjusted to account for differences in pharmacokinetics and in placebo effect.

As previously shown in adults with PO seizures, a drug-disease model can be used to describe seizure counts over time. Given our interest in the role of bridging and extrapolation principles in paediatric research and the somewhat limited patient pool, we have decided to apply the same model used for adults and older paediatric patients, despite conflicting views regarding the differences in the underlying pathology in this group of patients. We have assumed that structurally, the differences may be in parameters estimates, not in the way seizure frequency is parameterised in this model. In fact, the data was well described.

Since LMT has been used off label in this population, it remains unclear whether dose and dosing regimens are appropriate. Thus, in **Error! Reference source not found.** we provide dosing recommendations stratified for baseline seizure frequency. To achieve a 50% seizure reduction in a typical patient from our trial data, a LMT average daily concentration of only 1 mg/L is required, resulting in a dose of only 18 mg/day in a typical 1-year old patient. However, doses provided per stratified baseline seizure frequency show that, as the baseline seizure frequency increases, doses approach levels that may be high enough to lead to toxic effects. Doses to

achieve the same result in our previous study in adults with PO seizures are provided for comparison.

Table 3. Seizure frequency at the start of treatment is used as covariate for dose selection, based on the PK and PD of a typical adult weighing 70 kg derived from the earlier adult PD model, and a typical 1-year old patient weighing 10 kg derived from the current PD model. The earlier-presented PK model may be used for further dose personalisation, especially in toddlers and infants. Total doses may be rounded to 5 mg, as more accurate dosing differences may not easily be achieved using dosing tools based on lamotrigine oral suspension formulations currently available. Doses should be multiplied by 0.5 (halved) when given in combination with valproic acid, and multiplied by 1.76 for comedication with carbamazepine or 2.29 for comedication with phenytoin. Care should be taken not to go over the maximum total daily dose.

Seizure frequency (day^{-1})	Dose for adult PO seizures (mg/kg/day)	Dose for paediatric PO seizures (mg/day)
0.1	3	4
0.2	6	8
0.3	9	13
0.4-0.6	11-16	17-26
0.7-0.9	18-24	32-45

Our parameter results in **Table 2** clearly show that in addition to striking differences in pharmacokinetics, placebo effect is significantly different in young children. In addition, apparent differences were observed for EC_{50}, which was found to be lower than that in adults, showing that these young patients are possibly more sensitive to the effect of LMT. However, given that both values are within the same order of magnitude, it is not possible to establish the clinical relevance of such differences. On the other hand, it should be noted that the larger placebo effect in children has been previously reported in literature [20]. These similarities seem to suggest that estimates from adult patients may be used to support the dose rationale in young children, which has recently been taken up by the FDA, although this does not necessarily extend to patients younger than 4 years [21,22]. The fact that differences were found between adults and these young children show that overall response profiles may not necessarily arise from exactly the same parameter distributions. Whilst we have to

acknowledge the limited number of patients and the absence of further details on the companion drugs, these findings highlight the advantages of a parametric approach; empirical extrapolation may not be as effective. A comparison of parameters from adults with PO seizures to those in the current population is provided in **Table 2**.

Based on the aforementioned findings, it became evident that previously failed clinical trials may simply be a consequence of poorly designed studies. Clinical trial simulations showed that the original trial of LMT in patients aged 1-24 months old was statistically underpowered. Indeed, while statistically treatment response did not separate from placebo, the predicted effect size was found to be comparable to adults and quite clinically relevant, after correcting for the differences in pharmacokinetics. Statistical significance was shown to be reached by inclusion of at least 200 subjects in a study, assuming that dosing will be adjusted for the increased clearance in the population of interest. At the same time, our analysis suggests that paediatric doses may be derived based on bridging and extrapolation principles. These results also shed light into the requirements for the development of a model-based dosing algorithm, as similar principles should be applied to both populations.

We acknowledge that our investigation has some important limitations. First, it should be noted that the clinical trial simulations are based on a model built to describe seizure counts. We could not evaluate the impact of prior treatment or increase in severity. We also have account for the potential bias in estimates due to inclusion and exclusion criteria. Second, the limited number of patients on placebo (19 out of 177), may not have allowed sufficient precision and accuracy in estimation of the placebo effect. Third, our simulations were based on the parameters found in the only 38 subjects included in the double blind phase of the trial. Many more subjects were included during the open-label phase, although the results of the primary endpoint of the trial were not based on these other subjects.

Whereas a larger body of evidence may be required to confirm our findings, they provide an indication that LMT may be efficacious in this population, if patients are treated with the appropriate dose. As such, our methods may

provide a framework for the implementation of a common dosing algorithm across the overall population of patients with PO seizures. It also highlights the importance of endpoint selection and trial design requirements for establishing efficacy. In the field of epilepsy such issues are often undervalued and it is suspected that the use of suboptimal trial designs has led to many failures in showing superiority to placebo. As has been pointed out elsewhere, not only the choice of endpoint but also its statistical analysis has great implications for the validity of the outcome of a trial [6].

In conclusion, despite some limitations, the use of a drug-disease model allowed the characterisation of the exposure-response relationship of lamotrigine in patients younger than 2 years of age. Estimates suggest comparable disease-specific parameters between adults and young children, which provides the basis for further review of the role of bridging and extrapolation in this patient group. The doses and dosing regimens proposed here should be considered in future studies aimed at the evaluation of the efficacy and safety of lamotrigine in this subgroup of patients.

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