Levetiracetam Exposure-Response Analysis in Children with Partial Onset Seizures

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OBJECTIVES

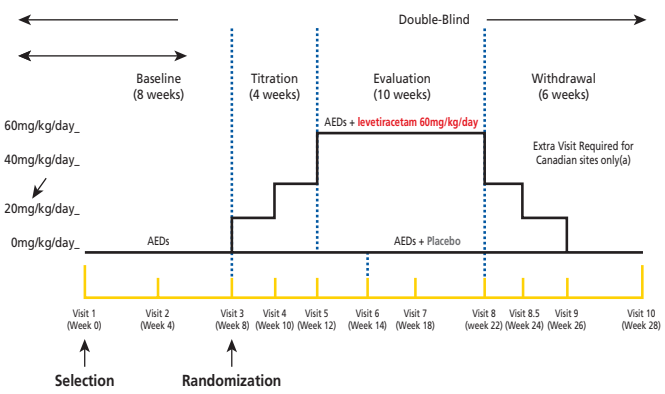
To compare the performance of several seizure count-based exposure-response models for levetiracetam in children with epilepsy, and to undertake simulations to provide a rationale for an optimal dosing scheme.

METHODS

Data were obtained from a randomized, double-blind placebo controlled, add-on efficacy trial of levetiracetam in children with partial onset seizures [1]. The trial consisted of an 8-week prospective baseline followed by two fixed dose up-titration periods at 20 and 40 mg/kg/day, an evaluation period of 10 weeks at 60 mg/kg/day or at the maximum tolerated dose, and a 6-week withdrawal period.

The dataset consisted of 195 subjects (95 placebo, 100 levetiracetam), with 31023 records. The median (range) demographic characteristics were: age 10 (3-17) years, body weight 34 (12-87) kg, baseline weekly seizure frequency 5.1 (0.5-698). Number of concomitant AEDs ranged from 1 to 4, with 49.7% of the patients taking 2 AEDs (not including levetiracetam).

Figure 1: Study Design



Modeling of daily seizures was performed by nonlinear mixed effects modeling in NONMEM VI with the Laplace estimation method. Several statistical models were compared: Poisson or negative binomial, with or without zero-inflation, and with or without Markov elements. The sequence of models was based on adaptations of earlier work by Trocóniz *et al* [2].

Poisson distribution $$P(DV) = \frac{\lambda^{DV}}{DV!}\exp(-\lambda)$$

(λ= expectation of the daily seizure rate)

Negative binomial distribution $$P(DV) = \frac{\Gamma(DV+\frac{1}{\alpha})}{\Gamma(\frac{1}{\alpha})\cdot DV!}\, p^{\frac{1}{\alpha}}.(1-p)^{DV}$$

(α=over-dispersion; p=1/(1+αλ))

Zero inflation was modeled assuming that zeroes in the data arise from a combination of a standard Bernoulli (0,1) process describing the probability of an extra zero, plus either the Poisson or Negative Binomial process.

A Markovian pattern was implemented by determining for each subject and for each day, whether the preceding day had either at least one seizure or none. Two baseline seizure rates *(Base)* were assumed with seizures occurring on the preceding day or not.

A Mixture model was used to separate the patients in two sub-populations exhibiting reduced (sub-population A) or increased (sub-population B) seizure frequency from baseline.

The drug effect was modeled in the sub-population A of improving subjects as an E_{max} function of dose or of AUCs (individual posterior estimates derived from a population pharmacokinetics model [3]):

$$E = \left(1 - \frac{EMD \,.\, D}{e^{\log ED_{50}} + D}\right) \cdot \left(1 - \Delta_{Placebo,A}\right)$$

where *EMD* is the maximum drug effect:

$$EMD = 1 - \frac{1 - E_{max}}{1 - \Delta_{Placebo,A}}$$

Inter-individual variability was added in a logistic regression-type equation:

$$I = \frac{e^{\log(E/(1-E)) + \eta)}}{1 + e^{\log(E/(1-E)) + \eta)}}$$

Finally, the estimated daily seizure count was given by:

$$\lambda = Base \,.\, I$$

where *Base* was the estimated seizure frequency throughout the baseline period, assumed to be log-normally distributed between individual subjects, *D* was the daily dose of levetiracetam (or plasma AUC), *EMD* was the maximum drug effect, E_{max} was the maximal fractional reduction in seizure frequency and ED_{50} was the daily dose in mg (or AUC in mg.h/L) producing 50% of maximum decrease in seizure frequency. The $\Delta_{Placebo,A}$ was the fractional change in seizure frequency from baseline after placebo treatment in improving subjects, and applied to treated subjects as well.

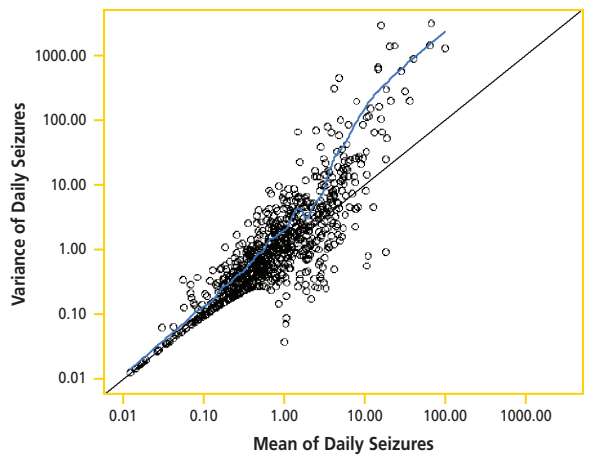
Sub-population B of patients deteriorating during treatment with levetiracetam or placebo, was modeled using similar equations, but *E* was equal to a single deterioration parameter, and the estimated daily seizure count was instead given by:

$$\lambda = Base \,/\, I$$

RESULTS

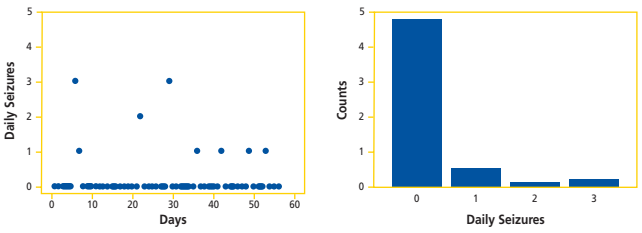
The Poisson distribution has the property that the mean is equal to the variance. **Figure 2** illustrates the higher than expected variance (over-dispersion).

Figure 2: Relationship between Mean and Variance of Daily Seizure Count



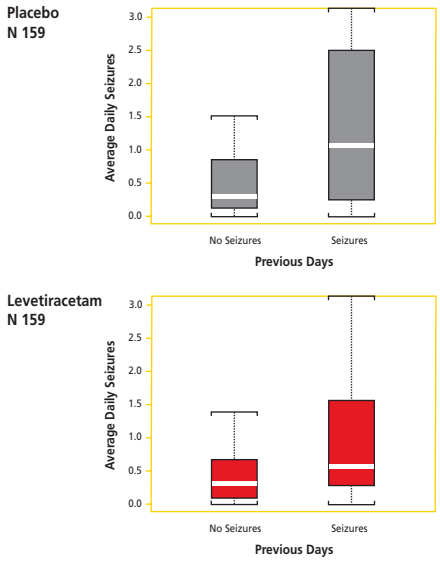
Zero-inflation was also present in the data as illustrated in **Figure 3**:

Figure 3: Daily seizures pattern and counts distribution in a typical subject



And, as illustrated in **Figure 4**, seizures were less likely to occur on days following a seizure-free day (Markovian feature):

Figure 4: Average Daily Seizures Frequency on Days Preceded or not by a Seizure-Free Day



The objective function values (OFVs) indicated a huge improvement when using a Negative Binomial over a standard Poisson model, followed by a further substantial improvement when incorporating a Markov process and finally a (relatively) smaller improvement when accounting for zero-inflation (**Table 1**).

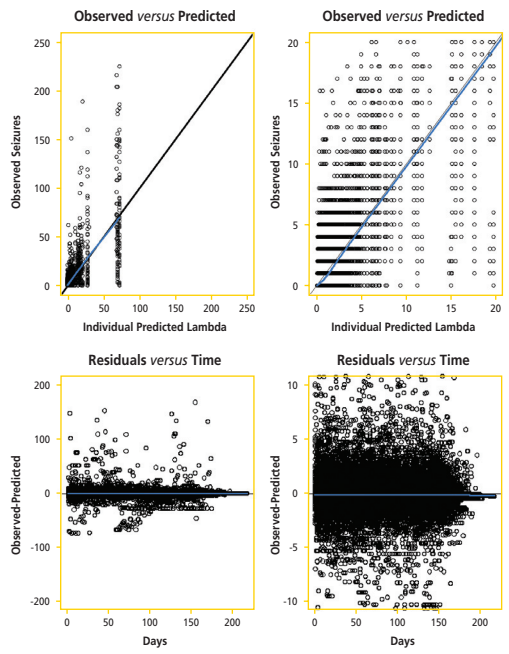
For the subset of subjects in whom AUC exposure estimates were available (96.6% of the full dataset), there was no improvement at all when using AUC instead of Dose.

Table 1: Objective Function Value for the Different Models

	Model	OFV	ΔOFV	Comment
Dose-response models				
1	Poisson	94965	0	
2	Zero-inflated Poisson	91537	-3428	
3	Negative Binomial	79182	-15783	
4	Zero-inflated Negative Binomial	79085	-15880	
5	Negative Binomial + Markov	78001	-16964	
6	Zero-inflated Negative Binomial + Markov	77904	-17061	Final model
Exposure-response models using available AUC estimates (96.6% of full dataset)				
7	Zero-inflated Negative Binomial + Markov	74838.20	0	Using Dose
8	Zero-inflated Negative Binomial + Markov	74838.06	-0.14	Using AUC

Observed daily seizure counts at baseline and following placebo or levetiracetam matched well with the predicted counts (**Figure 5**, upper left and right panels), and residual plots showed no trend over time (lower left and right panels). The left side shows the entire data set, while the majority of data excluding extreme seizure counts are plotted on the right side.

Figure 5: Goodness-of-Fit Plots for the Final Model



The parameters of the final model are gathered in **Table 2**. The baseline seizure frequency was 0.64/day when the previous day was seizure-free and 1.06/day (0.639+0.425) when one or more seizures occurred on the previous day. The improving sub-populations amounted to 78% and 52% of the levetiracetam and placebo groups respectively. The population ED50 was 287 mg/day.

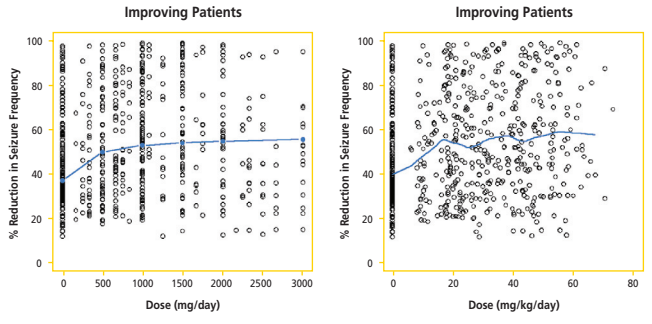
Table 2: Population Parameter Estimates of the Final Daily Counts Model

Parameters (SE CV%)	Improving patients	Deteriorating patients
Baseline seizure frequency (day-1) - No seizures previous day - Increase in frequency with one or more seizures on previous day	0.639 (16%) 0.425 (38%)	
√Ω [a] Baseline seizure frequency - No seizures previous day - One or more seizures previous day	107% 123%	
α (over-dispersion) P0 (zero-inflation)	0.356 (19%) 0.0157 (58%)	
Placebo		
Sub-population (fraction) Fractional change	0.52 -0.37 (27%)	0.48 (30%) 0.11 (-0.04 to 0.31)[b, c]
Levetiracetam		
Sub-population (fraction) Overall E_{max} (fractional change) ED_{50} (mg/day) Fractional change	0.78 0.57 (23%) 287 (46 to 1802)[c]	0.22 (36%) 0.11 (-0.04 to 0.31) [b, c]
√Ω[a] for improvement at ED_{50} √Ω[a] for improvement placebo[d] √Ω[a] for deterioration[e]	82% 45% 123%	

[a] √Ω: square root of the variance of the random effect, measuring inter-individual variability (%CV).
[b] The fractional increase in seizure frequency in deteriorating subjects is assumed to be similar in placebo- and levetiracetam-treated populations
[c] Estimated 90% confidence intervals
[d] At an improvement of 37%
[e] At a deterioration of 11%

Simulations by bootstrapping (using the observed body weights) showed that most of the drug effect was reached at 20 mg/kg/day (**Figure 6**) and that the clinical response in the range of 20-60 mg/kg/day in children was fairly similar to that of 1000-3000 mg/day in adults. Simulations predicted that levetiracetam 60 mg/kg/day is likely to result in a reduction in seizure frequency of at least 55% in half of the improving subjects.

Figure 6: Predicted Dose-Response Relationship in Improving Pediatric Patients for Levetiracetam Daily Dose in mg/day (Left Panel) and in mg/kg/day (Right Panel):



CONCLUSIONS

The zero-inflated negative binomial model with Markov elements has superior features for describing daily seizure count data. The daily levetiracetam dose of 20-60 mg/kg appears optimal in adjunctive therapy of children with refractory partial onset seizures.

References:

[1] Glauser TA, Ayala R, Elterman RD, Mitchell WG, Van Orman CD, Gauer, LJ, and Lu Z; on behalf of the N159 Study Group. Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures. *Neurology* 2006;**66**:1654-1660.

[2] Trocóniz IF, Miller R, Karlsson MO. Modelling overdispersion and Markovian features in count data. Abstracts of the Annual Meeting of the Population Approach Group in Europe. PAGE 16, 2007, abstr 1078 [www.page-meeting.org/?abstract=1078]

[3] Toublanc N, Sargentini-Maier ML, Lacroix B, Jacqmin P, Stockis A. Retrospective population pharmacokinetic analysis of levetiracetam in children and adolescents with epilepsy: Dosing recommendations. *Clin Pharmacokin* 2008;**47**:333-341.