Levetiracetam Exposure-Response Analysis in Children with Partial Onset Seizures

Eric Snoek*, Rik Schoemaker*, Armel Stockis**, Christian Ootul**, Maria Laura Sargentini-Maier**
*Expremo NV, Mechelen, Belgium; **Pharmacometrics Department, UCB Pharma SA, Braine-l’Alleud, Belgium

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. The trial consisted of an 8-week prospective baseline followed by two fixed dose up-titration periods at 20 or 60 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 3102 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).

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).

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

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:

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

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

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

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

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

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

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