Modeling the effect of levetiracetam on daily and aggregated seizure counts in adults and children

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Introduction

A population PK and PK/PD analysis using the population approach was conducted using data of levetiracetam (LEV) trials after bid oral dosing from both adult and pediatric subjects with partial onset seizures. The primary aim was to assess whether pediatric subjects are different from adults regarding the PK/PD relationship, i.e. the effect of LEV exposure on seizures. For adult subjects only aggregated seizures (in between monthly visits) were available, while daily seizure counts were available for pediatric subjects. The information on PK/PD differences between adults and children could be used to scale effects of anti-epileptic compounds (AEDs) with a similar primary mechanism of action from adults to children.

Objectives

- To determine the exposure-response (PK/PD) relationship between levetiracetam concentration and seizure counts in the adjunctive treatment of epileptic seizures in both pediatric and adult subjects.
- Assess potential differences in this relationship between adults and children that may be used to scale effects from adults to children for a drug with a similar primary mechanism of action.

Methods

A combined adult/pediatric PK/PD model was developed in analogy to a model developed for the AED brivaracetam [1], that described seizure counts using a negative binomial distribution, and using a mixture model to separate a 'responder' (*P*1) and a 'placebo like' (*P*2) sub-population, using material in part presented previously [2].

$$\log(S_{0ij}) = \log(S_0) + \eta_{1i} + \frac{(\log(S_{\max})+\eta_{2i})\cdot PDV_{ij}}{ES_{50}+PDV_{ij}}$$

$$\lambda_{ijP1} = e^{\log(S_{0ij})+Q2\cdot\left(\log(Placebo)+\eta_{3i}+\frac{\log(E_{\max})\cdot e^{\eta 4i}\cdot Cav_{ij}}{e^{\log(EC_{50})}+Cav_{ij}}\right)}$$

$$\lambda_{ijP2} = e^{\log(S_{0ij})+Q2\cdot(\log(Placebo)+\eta_{3i})}$$

For the pediatric subjects, daily seizure count diaries were available, and for the adults, aggregated seizure counts were recorded over between visit (4 weekly) periods. The daily seizure counts for pediatric subjects were described taking previous day seizure frequencies into account, and using inter-individual variability on over-dispersion.

For the aggregated adult seizure counts this level of detail was lost and therefore not incorporated. Expected values for total counts per period, for the adult subjects, were given by $\lambda\cdot$(number of days counted).

Visual predictive checks (VPCs) were used to ascertain the ability of the adult/pediatric PK/PD model to adequately simulate trial outcome using percentage change in seizure frequency from baseline, and fraction of subjects with ≥50% decrease in seizure frequency.

Simulations were performed to visualize the concentration-effect relationship between LEV exposure and change from baseline in seizure frequency.

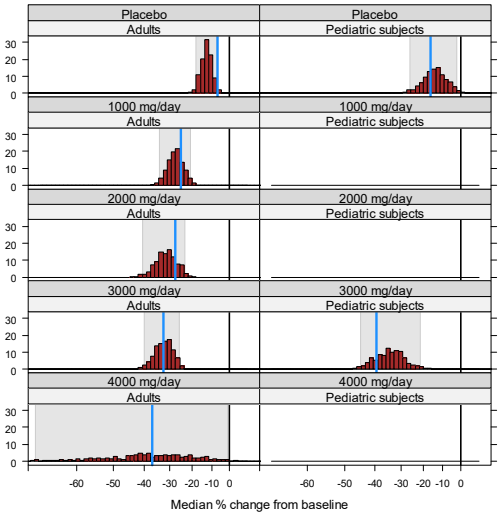
Modeling was performed using NONMEM 7.2.0.

Results

PK/PD model

The combined adult/pediatric PK/PD model was able to describe both the adult and the pediatric data using the same drug effect population parameters, and using a model structure very similar to the existing adult PK/PD brivaracetam model [1]. 33.5% of subjects were estimated to be in the 'mixture model responders' sub-population (see Table 1). VPCs illustrated that the adult/pediatric PK/PD model was capable of simulating the observed trial outcomes for both groups regarding both median percentage change from baseline (Figure 1) and fraction 50% responders: patients with ≥50% decrease in seizure frequency from baseline (Figure 2).

Figure 1. VPC for combined adult/pediatric PKPD model by dose and adults and pediatric subjects for median % change from baseline



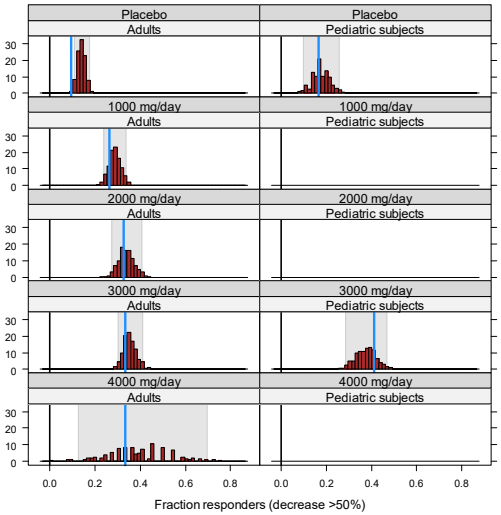
Histograms provide the distribution of outcomes for 500 simulated studies, the blue vertical line displays the result for the observed data, and gray areas encompass 95% of simulated study outcomes. The 3000 mg/day dose identifier for pediatric subjects indicates the active treatment arm where the 60 mg/kg maintenance dose corresponds to 3000 mg/day for adult subjects

Table 1. NONMEM parameter estimates for the final LEV PK/PD model

Parameter	*Estimate (95% CI)*	*SE (%CV)*	*IIV (%)*
S_0 Adults (day^{-1})	0.337 (0.317/0.360)	3.0%	86.9%
ES_{50} (seizures)	2.75 (2.49/3.01)	4.8%	
S_{max} (% increase)	260.2% (238.1%/283.7%)	2.5%	119.8%
Placebo (% change)	-14.8% (-18.7%/-10.7%)	15.1%	40.7%
E_{max} (% change)	-95.6% (-99.7%/-29.0%)	45.4%	80.0%
EC_{50} (mg/L)	31.4 (6.34/156)	23.7%	
OVDP	0.107 (0.0907/0.125)	3.6%	291.0%
Box-Cox parameter on S_0	0.442 (0.367/0.517)	8.7%	
Mixture fraction*	0.335 (0.252/0.418)	12.7%	
S_0 (% change) pediatric subjects	52.2% (31.2%/76.6%)	18.0%	

*fraction of subjects in the mixture-model responder population

Figure 2. VPC for combined adult/pediatric PKPD model by dose and adults and pediatric subjects for fraction 50% responders (patients with ≥50% decrease in seizure frequency from baseline)



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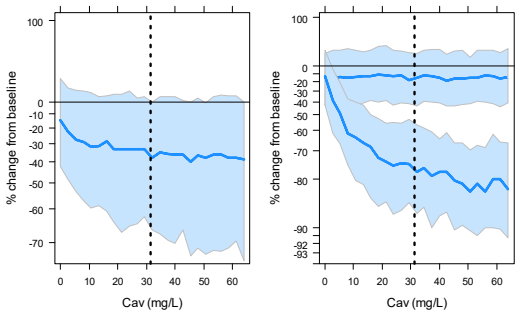
No drug related differences in the PK/PD response for LEV between adults and pediatric subjects were detected. As a consequence, the combined model can be used to obtain predictions of seizure response in pediatric subjects, for an AED with a similar primary mechanism of action.

Simulations

Daily seizure count sequences for LEV in pediatric subjects, with dependence on preceding-day seizures, could be simulated using NONMEM, showing that the model had good simulation properties.

The left panel of Figure 3 provides the median of the predicted individual percent changes from baseline for the final LEV PK/PD model, without distinguishing between the mixture model placebo like population and the mixture model responder population. The blue area provides the range of outcomes for 50% of the subjects to illustrate the huge variability in response. By averaging over both populations, the sizeable gain for the fraction of subjects that provides a clear response is hidden; the right panel of Figure 3 provides the same graph but split by mixture model population.

Figure 3. Overall simulated LEV effect by LEV Cav (left) and split by mixture model population (right)



Median (blue line) and interquartile range (light blue area) of simulated individuals; vertical dotted line: EC_{50}

Conclusion

- The combined adult/pediatric PK/PD model showed that no scaling was needed for drug related PD parameters between adults and children.

References

[1] PAGE 24 (2015) [www.page-meeting.org/?abstract=3559]
[2] PAGE 17 (2008) [www.page-meeting.org/?abstract=1403]

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