The Established Status Epilepticus Treatment Trial: A PK simulation study to assess feasibility of a sparse blood sampling approach to estimate FOS, VPA, and PHT exposures in children

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Rationale

The Established Status Epilepticus Treatment Trial (ESETT) is a randomized, double-blind clinical trial comparing fosphenytoin (FOS), levetiracetam (LEV) and sodium valproate (VPA) in patients with established status epilepticus (ESE). An ancillary study (ESETT PK-PD) will characterize how plasma concentrations of these 3 drugs relate to the likelihood of seizure cessation in children using exposure-response modeling. To do this, an individualized estimate of early drug exposure is required, but enrollment of children in an emergency setting limits the amount of blood per sample and the number of samples that can be collected. Hence, this study utilizes a sparse sampling approach: 1 sample collected within 20-50 min and the other between 60-120 min after the start of study drug infusion. The objective of this work is to characterize the performance of a sparse sampling approach to predict concentrations at 60 min (C60) and partial AUCs from 20-120 min (pAUC) post start of drug infusion in a simulated patient population generated from literature-based models for FOS, LEV, and VPA.

Methods

Literature-based population PK models were used to simulate samples from 500 pediatric patients (8 to 75 kg) with rich concentration-time profiles (ie. “true”) for each study drug (20 mg/kg phenytoin-equivalents FOS, 40 mg/kg VPA, or 60 mg/kg LEV intravenous infusions over 10 minutes). One timepoint and corresponding concentration was randomly selected from each of the two sampling windows (20-50 min and 60-120 min after the start of study drug infusion) for 100 randomly selected simulated patients with replacement. We then developed population PK models using these 200 total concentrations from the 100 simulated patients (2 drug concentrations per subject). The PK model used was one-compartment for FOS and VPA and two-compartment for LEV. The sparse-sampling model-predicted pAUC and C60 were correlated with the “true” pAUC and C60 (reference) values from the full set of simulated data. As an alternative approach, the concentration at the randomly sampled timepoint in the first window C1(20-50min) was also compared with C60. R was used for simulations (mrgsolve), statistical analyses and graphing and NONMEM v 7.3 (Non-Linear Mixed Effects Modeling Software, Icon Ltd) was used for PK population modeling.

Results

Despite using a mg/kg dosing scheme in children, approximately 3-fold variability in predicted exposure measures was found for all 3 drugs. For the sparse sampling approach, good correlation between the predicted pAUC and C60 and the “true” pAUC and C60 was observed with correlation coefficients (R) of 0.7-0.9 for all 3 drugs ($p << 0.001$). Using C1(10-50min) as an estimate of C60 was inferior to the sparse-sampling population modeling approach (R= 0.76, 0.54, and 0.43 for FOS, VPA, and LEV, respectively).

Conclusions

We conclude that a sparse sampling approach can accurately predict metrics of early drug exposure. Simulations show that we expect approximately 3-fold variability in drug exposure which aligns well with the results from the sparse sampling model. The use of sparse PK sampling will allow for exposure-response modeling which will enable further investigation of factors affecting drug response in children with ESE when blood sampling is limited. This approach can be explored in other emergent conditions and/or in children when blood sample limitations exist.

I don’t know if the figures sent in the separate PowerPoint were going to be included in the abstract submission. If so, the abbreviations should be reconciled, i.e., pAUC rather than AUCpred, C60 rather than Conc upto 1hr or IPRED at 1hr, etc. All horizontal axes should be labeled simulated and all vertical axes should be labeled predicted.