ESETT PHARMACOKINETIC-PHARMACODYNAMIC (PK/PD) STUDY RESULTS

Lisa Coles - University of Minnesota
Outline

• Study overview
• Lessons
• Study Results
• Simulation Study
ESETT PK/PD Study

Aim: Relate drug exposure (area under the curve) with seizure cessation and the key secondary outcomes.
Study Timeline

- ESETT started enrolling Nov. 2015
- Adult enrollment closed Oct. 2017
- ESETT closed – Dec. 2018

- PK-PD study funded – 8/15/2017
- 1st enrollment – 11/6/2017
- 27 children enrolled (~50% of eligible ESETT patients)
  - FOS -11
  - LEV – 7
  - VPA- 9
Lessons learned

- **Challenges adding PK to ongoing study**
  - Potential ESETT patients lost because sites initiations were rolling
  - Integrate blood sampling into the ESETT procedures
  - Continuous communication with sites critical
- **Consent often required for children**
- **Blood collection challenges**
  - Too restrictive blood sampling protocol
  - If a first sample was collected, second was also obtained.
  - Make PK sampling and sample processing procedures simple
- **Sites were committed to obtaining PK samples**

![Reasons for Missed Enrollment](Image)
**PHT Concentrations**

- N = 11
- Large intra-subject variability
- 81-94% bound
VPA Concentrations

- N = 9
- 48-82% bound
LEV Concentrations

- N= 7
- High between-subject variability
Effect of Weight and Dose on Seizure Cessation

• Weights of 247 adults: 36-157 kg
• 122 weighed > 75 kg
• Overall success rate: ~43% in those < 75 kg ~39% in those >75 kg
• Success rates for LEV: 40% and 41%, VPA: 41% and 47%, and FOS: 40% and 41%
• No statistically significant differences in seizure cessation using dose/weight as primary predictor
Summary of Findings

- In children, no strong evidence that drug concentrations help explain treatment response
- In adults, weight-based dosing with a 75 kg cut-off did not appear to have an effect on treatment success
- Small sample size limits our ability to draw conclusions
PK Simulation Study

- PK/PD study objective was to relate early drug exposure (concentrations) with response
- Sparse sampling approach (20-50 min and the other within 60-120 min after the start of drug infusion)

- Objective: evaluate the performance of this sparse sampling approach to predict partial area under the curve from 20-120 min (pAUC) using a simulated patient population generated from literature-based models for PHT, LEV, and VPA.
Simulation Study to Evaluate Feasibility of Sparse PK Sampling Approach

PK simulations using literature-based population PK models
- 100 patients simulated
- 8-75 kg
- mg/kg ESETT doses
- Rich conc-time profiles

“True” data rich concentration-time profiles

“Real world” rich concentration-time profiles
Randomly select one timepoint/conc from each sampling window
Set of 100 simulated patients with 2 data points each

Build Population PK Model
Predict individual pAUC

PPE for pAUC = \[ \left( \frac{\text{Sparse pAUC} - \text{Simulated(true) pAUC}}{\text{Simulated(true) pAUC}} \right) \times 100 \]
Simulation Results

- Good correlation between “true” and predicted “sparse” drug exposure pAUCs.

- The percent prediction error was within ± 20% in most cases for all 3 drugs.
Summary of Findings

• Sparse sampling approach can accurately predict metrics of early drug exposure.
• Allow for exposure-response modeling to investigate factors affecting drug response.
• This approach can be explored in other emergent conditions and in children when blood sample limitations exist.
Thank you from the ESETT PK-PD Study Team!!