RESEARCH/PROJECT NAME: Comparison of Whole Blood and Plasma Topiramate Concentrations in Children

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CURRENT STATUS/TIMING: Recruiting

OVERALL GOAL: Correlate whole blood, dried blood spot, and plasma concentration of topiramate in children

PROJECT SUMMARY:

Topiramate (TPM) is an FDA-approved oral antiepileptic drug for adults and children 2 years and older.
The goal of this research project is to determine if dried blood spots (DBS) technology can be used to measure TPM concentrations. Additionally, this project will compare whole blood, DBS, and plasma TPM concentrations in children and characterize TPM pharmacokinetics in each matrix. The problem with using DBS to measure TPM levels is that it exhibits saturable binding to carbonic anhydrases in red blood cells resulting in non-linear relationship at low, but clinically relevant, plasma concentrations. Published reports converting whole blood or DBS TPM concentrations into plasma levels appear to have neglected to properly account for this non-linear binding. We are measuring TPM concentrations using LC-MS in pediatric patients (ages 5-12) who are on maintenance TPM therapy. One (2 ml) blood sample will be collected from venipuncture and one sample from a finger-prick for DBS from each of the 24 patients. Ideally, the one blood sample from each patient will occur during these times points: 0-2 hours, 2-4 hours, 4-6 hours, and 6-8 hours after last dose. TPM concentrations measured in whole blood, DBS, and plasma samples will be compared using weighted Deming regression. Plasma concentrations will be calculated from the whole blood or DBS concentration. Calculated plasma and analyzed plasma samples will be compared using the Bland and Altman plot. Acceptable criteria for the agreement between calculated and analyzed plasma concentrations will be based on the Bioanalytical Method Validation FDA guideline, which stipulates that the difference in concentration should be with ±20% of their mean for at least 67% of the samples. Population estimates for clearance and distribution volume will by calculated using non-compartmental analysis (Phoenix WinNonLin, Pharsight®) of TPM concentration-time data. Given the sparse pharmacokinetic sampling design, a non-linear mixed effects modeling approach will also be applied for analysis (NONMEM, Phoenix NLME). Understanding the relationship between whole blood and plasma TPM concentration permits accurate estimation of plasma TPM levels in adults and children and can help guide optimization TPM therapy. Further, a reliable and validated DBS assay would reduce the volume needed from patients, which is particularly significant for young children and would also facilitate out-of-hospital collection of blood samples for therapeutic drug monitoring.