Therapeutic Drug Monitoring of Antiepileptic Drugs During Pregnancy

James C. Ritchie¹, Patricia Scott-Harrell¹, Clay Ramsey¹, Richard Lukacin²

¹Emory University School of Medicine, Department of Pathology & Laboratory Medicine, Atlanta, GA 30322, ²Chromsystems Instrument & Chemicals, GmbH, 82166 Gräfelfing/Munich, Germany

Abstract

Background
Epilepsy is the most frequent neurological disorder worldwide with a prevalence of approximately 0.5% in western countries. Around one quarter of people with epilepsy are women of reproductive age and most of them use antiepileptic drugs (AEDs) for adequate control of their seizures. Additionally, AEDs are also used for the treatment of a broad range of other medical conditions such as bipolar disorders, cancer, neuropathic pain, anxiety disorders and migraines. Recent clinical studies have revealed that physiologic changes during different stages of pregnancy may lead to altered pharmacokinetics (especially altered clearance) for AEDs and broad individual variations which can result in difficulty predicting appropriate drug dosages. It is also well known that fetal drug exposure to some older AEDs (e.g., valproic acid) increases the risk of congenital malformations. Therefore, therapeutic drug monitoring (TDM) for AEDs should play an important role in the management of patients on these medicines who become pregnant. Here, we describe the measurement of a wide variety of AEDs in two groups of pregnant women (epileptics and bipolar).

Methods
We measured serum AED levels once per month through out pregnancy in both groups using a commercially available mass spectrometry kit (MassTox TMD Series A) from Chromsystems (Gräfelfing/Munich). The assay system is capable of measuring 26 different AEDs utilizing a single set of standards and a common extraction protocol. Samples are then chromatographed on one of five HPLC gradients and analysis by MS/MS. For each drug we plotted the dose to plasma concentration curve and calculated apparent clearance and relative clearance.

Results
Dose to plasma concentration correlations varied widely between the different drugs. Almost all the drugs showed an increased clearance in the second and third trimester. This was true even for the use of the AEDs in bipolar patients where the drugs are used at much lower concentration as adjunct therapy.

Conclusions
This pilot study demonstrates the utility of TDM of antiepileptic medications throughout pregnancy and highlights the use of LC-MS/MS in performing these measures. Additionally, the multiplexed MRM assay used in the study allows for the analysis of several different AEDs in a single run adding efficiencies of staffing and instrument times in the process.