Therapeutic Drug Monitoring of Antiepileptic Drugs During Pregnancy

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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 (***Mass****Tox*® TDM 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.

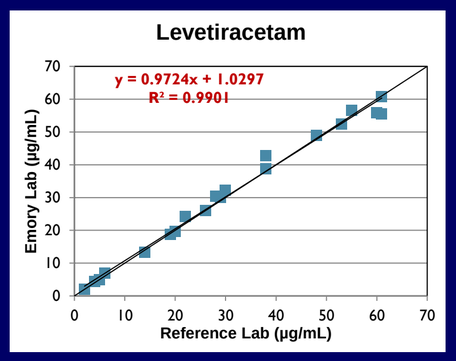
Conclusions

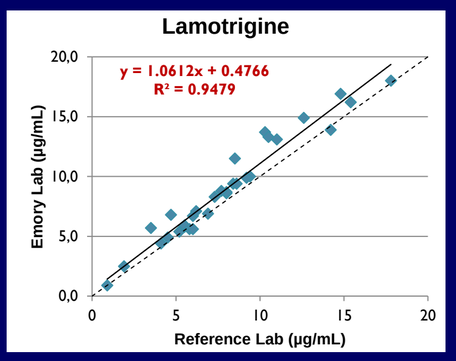
This pilot study demonstrates the utility of TDM of antiepileptic medications throughout pregnancy and highlights the use of LC-MS/MS in performing these measures. Additionally, the multiplexed MRM assay used in the study allows for the analysis of several different AEDs in a single run adding efficiencies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

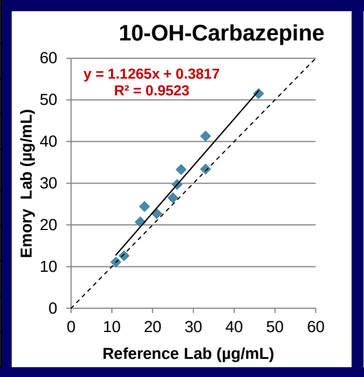
Results

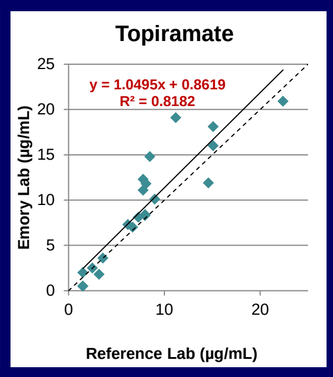
Precision			
	Concentration	Intra-assay	Inter-assay
	µg/mL	% CV	% CV
Group 1			
Carbamazepine	3.20	2.50	4.00
Carbamazepine-10,11-epoxide	0.95	4.50	7.20
Carbamazepine-diol	1.10	6.90	8.30
10-OH-Carbamazepine	8.25	4.00	7.50
Oxcarbazepine	0.30	6.25	15.10
Group 2			
Lacosamide	1.98	7.20	11.00
Lamotrigine	3.05	3.10	6.80
Levetiracetam	16.00	3.60	6.65
Group 3			
Gabapentin	4.30	2.52	5.20
Topiramate	3.28	4.60	6.85
Group 5			
Zonisamide	9.30	2.50	5.10

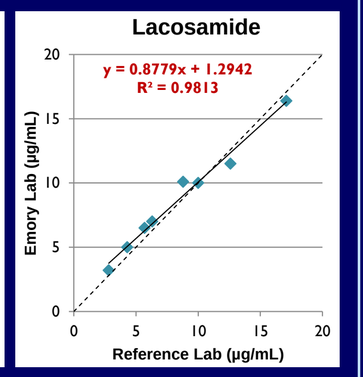
Assay Comparisons











Results

Assay Description

Mass*Tox*® **TDM Series A System**

Kit consists of 3 components
The BASIC Kit A
MasterColumn® A
13 Parameter Sets (more than 150 analytes)
AED parameter set allows for the LC-MS/MS MRM measurement of 26 drugs

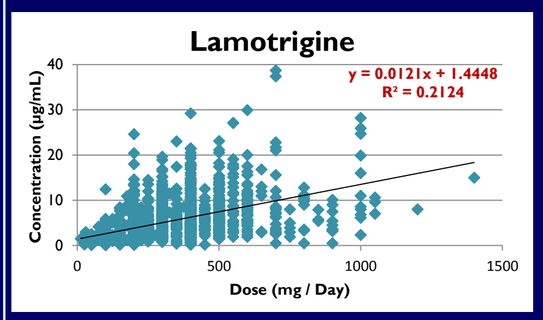
Set up on a Waters TQD and an AB Sciex 4000 Q Trap
4 Point calibration curves
2 Mass transitions per drug (except 2) and Internal Standards
18 AED Internal Standards
3 Gradient Protocols
3.5 Minute run times for all drugs

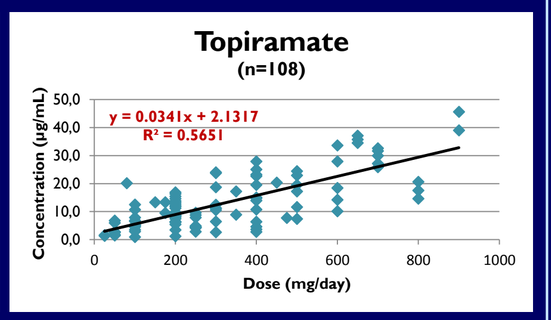
Common procedure for all compounds

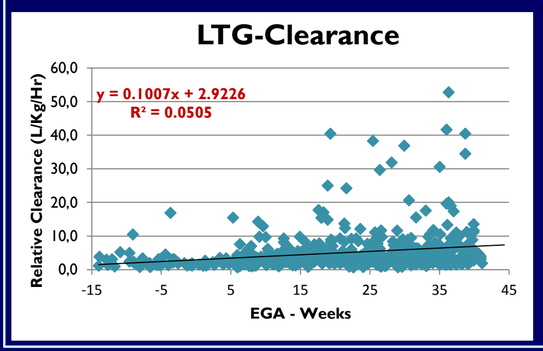
50 µL Sample/Calibrator/Control
25 µL Extraction Buffer, vortex, incubate 2 min.
250µL Internal standard mix (contains precipitation reagent)
Vortex, centrifuge 5 min at 15,000 x g
Dilute supernatant with buffer (group dependent)
Inject into the LC-MS/MS System

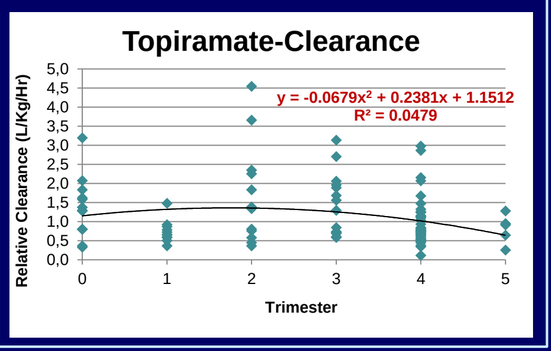
	LOQ	Reference Range	Linear Range
Group 1	µg/mL	µg/mL	µg/mL
Carbamazepine	0.2	4 to 10	0.2 to 16
Carbamazepine-10,11-epoxide	0.1		0.1 to 10
Carbamazepine-diol	0.2		0.2 to 10
10-OH-Carbamazepine	0.5	10 to 35	0.5 to 50
Oxcarbazepine	0.1	0.4 to 2	0.1 to 10
Group 2			
Felbamate	2.0	20 to 10	2.0 to 100
Lacosamide	0.2	1 to 10	0.2 to 12.5
Lamotrigine	0.2	2 to 10	0.2 to 30
Levetiracetam	1.0	10 to 40	1.0 to 100
Rufinamide	0.5	5 to 30	0.5 to 60
Theophylline (children)	1.0	2 to 8	1.0 to 60
Group 3			
Gabapentin	0.5	2 to 10	0.5 to 30
Pregabalin	0.2	2 to 5	0.2 to 30
Vigabatin	0.6	2 to 10	0.6 to 50
Sultiam	0.1	2 to 8	0.1 to 30
Tiagabine	0.0	0.02 to 0.2	0.01 to 0.8
Topiramate	0.5	2 to 10	0.5 to 30
Group 4			
N-Desmethylmesuximide	0.5	10 to 40	0.5 to 50
Phenytion	0.2	10 to 20	0.2 to 50
Primidone	0.2	5 to 15	0.2 to 25
PEMA	0.2	7 to 10	0.2 to 50
Stiripentol	0.5	1 to 6	0.5 to 30
Group 5			
Ethosuximide	2.0	40 to 100	2.0 to 150
Phenobarbital	1.0	10 to 40	1.0 to 60
Valproic Acid	5.0	40 to 100	5.0 to 150
Zonisamide	0.5	5 to 35	0.5 to 60

Patient Results









Conclusions

1. Clearance changes during pregnancy can lead to sub-therapeutic plasma levels of the AEDs
2. Pregnancy thus warrants a special case for the TDM of these medications
3. As the numbers of these drugs seems to be ever increasing, a multiplexed assay strategy for their measurement seems appropriate

Thanks to our patients for their participation.