BACKGROUND
Chemically, topiramate (3,4-dioxisopropylidene-D-β-fructofuranosyl sulfamate) is a sulfamate-substituted monosaccharide, related to fructose. It is used as both an anticonvulsant and an antiepileptic drug. Topiramate is frequently administered with other antiepileptic drugs (AEDs) such as phenytoin and carbamazepine. Pharmacokinetics varies widely, particularly with co-administration of other medications, age, and/or compromised renal function. For example, topiramate is eliminated at a faster rate in children, the magnitude of the increase in clearance compared to adults ranges in different studies from 25% to 170%. Also, the use of enzyme-inducing antiepileptic drugs (AEDs) such as phenytoin and carbamazepine gives rise to an increased metabolism of topiramate. The additional metabolism is capable of producing a 50% decrease in plasma concentration compared with patients receiving non-enzyme inducing AEDs. The faster elimination rate in children and in coadministered AEDs on the plasma concentration of topiramate make monitoring even more important due to the variability of dose administration.

OBJECTIVE
To evaluate the performance of the new ARK Topiramate Assay on the Roche/Hitachi 917 automated clinical chemistry analyzer.

METHODS
The ARK Topiramate Assay is a homogeneous enzyme immunoassay for quantifying topiramate in human serum or plasma. The assay was evaluated on the Roche/Hitachi 917. The assay was calibrated using a six point calibration curve (0 to 40.0 µg/mL). Limit of quantitation was evaluated according to CLSI/NCCLS EP17-A. Pooled human serum was supplemented with known amounts of topiramate (approximately 5.0 and 20.0 µg/mL). Accuracy (analytical recovery) was performed by adding concentrated topiramate drug (USP) into human serum negative for topiramate. Test sample concentrations were 1.5, 2.5, 5.0, 6.0, 10.0, 15.0, 20.0, 30.0, 45.0, and 55.0 µg/mL. Two analytical runs of three replicates of each sample were assayed. The results of the six replicates were averaged and compared to the theoretical target concentration. The percentage recovery was calculated. The amount of topiramate recovered from nominal range was from 95.1% to 107.1%.

RESULTS
Using a 20-day protocol (2 runs per day, quadruplicate measurements) total (within-lab) precision for the lower control was 4.3% CV (24.2 µg/mL), 2.7% CV (10.2 µg/mL), and 3.2% CV (6.2 µg/mL). The within-run precision component was 3.5% CV, 2.4% CV and 2.9% CV, respectively. Analytical sensitivity or Limit of Quantitation (LOQ) was 1.0 µg/mL. The assay was linear from 0.6 to 60.0 µg/mL, determined with samples prepared by serial dilution. Accuracy as analytical recovery was 95.6% to 107.1% for nominal values 1.5 to 55.0 µg/mL. Endogenous substances and commonly co-administered drugs did not interfere with measurement of topiramate at the levels tested. Using Passing-Bablok regression analysis for method comparison, ARK = 0.99 FFA = 0.17 (2 = 0.98, n = 16, range 10 to 59.1 µg/mL).

Analytical Recovery
Accuracy (analytical recovery) was performed by adding concentrated topiramate drug (USP) into human serum negative for topiramate. Test sample concentrations were 1.5, 2.5, 4.0, 5.0, 6.0, 10.0, 15.0, 30.0, 45.0, and 55.0 µg/mL. Two analytical runs of three replicates of each sample were assayed. The results of the six replicates were averaged and compared to the theoretical target concentration and the percentage recovery was calculated. The amount of topiramate recovered from nominal range was from 95.1% to 107.1%.

Linearity
Linearity studies were performed as suggested in CLSI/NCLLS Protocol EP6-A. Negative pooled human serum was supplemented with topiramate to give 60.0 µg/mL and then diluted proportionally. The assay was considered linear when the percentage difference between the predicted 1st order and 2nd order polynomial was within 10%. The assay was linear for individual dilution segments (0.6 to 6.0 µg/mL and 6.0 to 60.0 µg/mL). Regression plots of observed versus expected concentrations are shown for the entire linear range determined on the Roche/Hitachi 917, 1.2 to 540.0 µg/mL.

Specificity
A high-concentration of each compound was spiked into normal human serum with known levels of topiramate (approximately 5.0 and 20.0 µg/mL) and assayed along with a serum control of topiramate. Measurement of topiramate resulted in ≤10% error in the presence of drug compounds at the levels tested. The following compounds did not interfere with the measurement of topiramate at the levels tested.

Conclusions
The ARK Topiramate Assay System is FDA-Cleared, Licensed in Canada, and CE Marked. Performance was demonstrated on the Roche/Hitachi 917 System. The assay has an extended calibration range (0 to 60 µg/mL). Performance of the assay showed good precision, accuracy, specificity and linearity with excellent correlation to FPIA. The ARK Topiramate reagents, calibrators and controls are provided in liquid form ready-to-use.

INTENDED USE
The ARK Topiramate Assay is a homogeneous enzyme immunoassay intended for the quantitative determination of topiramate in human serum or plasma using an automated clinical chemistry analyzer. The results obtained are used in the diagnosis and treatment of topiramate overdose and in monitoring levels of topiramate to help ensure appropriate therapy.

ASSAY RANGE
The range of the assay is 1.5 to 540 µg/mL. Report results below this range as ≤15 µg/mL, or below the analyser-specific lower LOD established in your laboratory. Report results above this range as >340 µg/mL or above the analyser-specific upper LOD established in your laboratory.

Precautions

1. The ARK Topiramate Assay is not recommended for use in patients with renal impairment.

2. The ARK Topiramate Assay is not recommended for use in patients with hepatic impairment.

3. The ARK Topiramate Assay is not recommended for use in patients with HIV/AIDS.

4. The ARK Topiramate Assay is not recommended for use in patients with cancer.

5. The ARK Topiramate Assay is not recommended for use in patients with cardiovascular disease.

6. The ARK Topiramate Assay is not recommended for use in patients with diabetes.

7. The ARK Topiramate Assay is not recommended for use in patients with hypertension.

8. The ARK Topiramate Assay is not recommended for use in patients with obesity.

9. The ARK Topiramate Assay is not recommended for use in patients with asthma.

10. The ARK Topiramate Assay is not recommended for use in patients with allergy.

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