

Measurement of Levetiracetam in Serum or Plasma by Homogeneous Immunoassay

Background Information

Levetiracetam (Keppra, UCB Inc, Smyrna, Ga.) is an anti-convulsant drug available in the United States since 2000. The drug's initial FDA-approved indication was for adjunctive therapy of partial-onset seizures in adults, but additional indications have been subsequently approved. It has excellent oral bioavailability (>95%) and is renally excreted, with 66% of the drug present in urine unchanged, and 24% present as the primary metabolite, which is pharmacologically inactive. Hepatic metabolism of the drug has not been demonstrated, so changes in cytochrome P450 expression levels and activities, as well as interactions with other drugs, are unlikely. Plasma half-life of levetiracetam in otherwise healthy individuals is 6-8 hours.

High performance liquid chromatography (HPLC) of extracted samples has been available as a monitoring methodology for several years. In 2009, a 510(k) FDA-cleared, homogeneous immunoassay for levetiracetam monitoring in serum and plasma was introduced, with advantages that include reduced turnaround time and sample preparation, leading to potential improvements in patient care.

Clinical Indications

Although levetiracetam is recognized for its ease of dosing and tolerability, monitoring serum/plasma concentrations may be indicated in patients with conditions that often alter pharmacokinetic characteristics, such as renal impairment, pregnancy, or older age. Monitoring also may be useful to optimize regimens in individual patients, to guide dosing in newer extended-release formulations, or to investigate therapeutic failure or compliance.

Interpretation

Results are reported in units of $\mu\text{g/mL}$ (micrograms/mL). The Lab Test and Diagnostic Procedure Handbook (Lexi-Comp) reports a therapeutic range of 5-45 $\mu\text{g/mL}$ (approx 29-265 $\mu\text{mol/L}$) when levels are obtained to evaluate for poor clinical response, signs of toxicity, onset of seizures, changes in concurrent medication, or suspected noncompliance.

Limitations of the Assay

Serum or plasma specimens may be stored up to one week refrigerated; if testing is delayed beyond one week, specimens may be stored frozen up to four weeks. To optimize individual patient care, specimens from the same matrix should be used for tracking and/or result comparisons. Interference by other anti-epileptic drugs and the primary metabolite of levetiracetam (ucbL057) was evaluated by the immunoassay manufacturer and found to be minimal.

Methodology

The levetiracetam immunoassay (ARK Diagnostics, Sunnyvale, Calif.) was adapted for use on the ADVIA 1200 automated chemistry analyzer (Siemens Healthcare Diagnostics, Deerfield, Ill.). This platform allows for random access analysis and small sample volumes. The immunoassay is homogeneous and utilizes an antibody against levetiracetam. The reagents include levetiracetam labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH), which competes with analyte from the patient specimen for binding to the antibody. Antibody binding to the labeled drug-enzyme complex reduces the enzyme activity. Increased concentration of drug from the patient specimen, therefore, results in increased activity of (unbound) drug-enzyme complex. The reaction converts NAD to NADH, which is monitored spectrophotometrically.

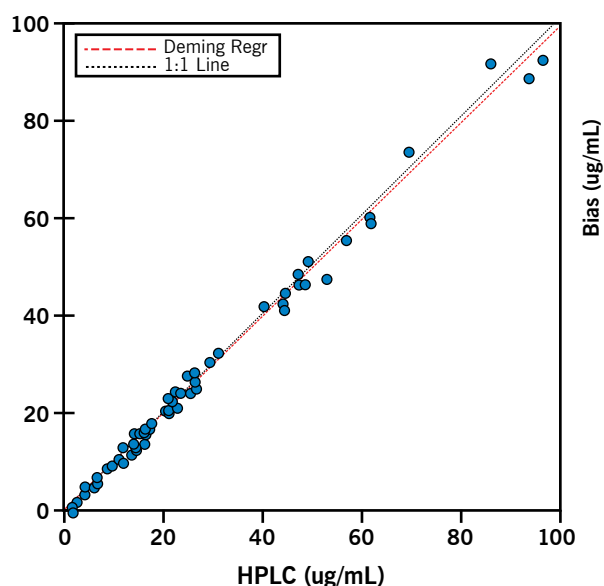
A method comparison between the new immunoassay and HPLC-UV as a reference method was carried out using leftover specimens from patients on levetiracetam therapy. As illustrated in figure 1, the immunoassay correlated very well with the HPLC-UV data (slope=0.982, $r=.9965$, $n=63$ samples).

Related Tests

Assays for monitoring many other anti-epileptic drugs are available and may be ordered in conjunction with levetiracetam concentration. Additional tests require larger sample volumes.

Suggested Reading

1. http://www.ark-tdm.com/pdfs/MKT09-003_Rev02_v04_ARKLevetiracetamDS_091216.pdf.



2. Crepeau AZ, Treiman DM. Levetiracetam: a comprehensive review. *Expert Rev Neurother*. 2010 Feb;10(2):155-7.
3. Johannessen SI, Tomson T. Pharmacokinetic variability of newer antiepileptic drugs: when is monitoring needed? *Clin Pharmacokinet*. 2006;45(11):1061-75.
4. Johannessen SI, Battino D, Berry DJ, Bialer M, Kramer G, Tomson T *et al*. Therapeutic drug monitoring of the newer antiepileptic drugs. *Ther Drug Monit*. 2003 Jun;25(3):347-63.
5. Matar KM. Quantification of levetiracetam in human plasma by liquid chromatography-tandem mass spectrometry: application to therapeutic drug monitoring. *J Pharm Biomed Anal*. 2008 Nov 4;48(3):822-8.
6. Curtis EG, Patel JA. Enzyme multiplied immunoassay technique: a review. *CRC Crit Rev Clin Lab Sci*. 1978;9(4):303-20.
7. Reineks EZ, Lawson SE, Lembright KE, Wang S. Performance Characteristics of a New Levetiracetam Immunoassay and Method Comparison with a High Performance Liquid Chromatography Method. *Therapeutic Drug Monitoring*. 33(1):124-7, 2011.

Test Overview

Test Name	Levetiracetam
Reference Range	5.0-45.0 $\mu\text{g/mL}$
Patient Preparation	For trough level, draw prior to next dose; for peak level, draw 1.0-1.5 hours after oral dosing
Specimen Requirements	Serum or plasma (EDTA or heparin) without gel separator; Minimum volume: 0.05 mL
Ordering Mnemonic	LEVIT
Billing Code	82491
CPT Code	82491

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