Methadone (Dolophine) is an opioid receptor agonist with analgesic and pharmacologic properties similar to morphine. It can be administered orally and provides analgesia for approximately 24 hours. The l-racemate of the drug is active, while the d-racemate has little activity. Methadone has properties that make it useful for treating heroin addiction. Sedation ensues with higher doses, which is an undesirable side effect. Administered in small doses of 5-20 mg, the drug occupies the opioid receptor for prolonged periods, blocking the action of morphine, precluding the euphoric effect that heroin addicts seek. Addicts who self-administer heroin while taking methadone experience no effect from the heroin, and addicts who take large methadone doses do not experience euphoria, only sedation, miosis, respiratory depression, hypotension, and dry-mouth. Tolerant patients may require doses of 60-100 mg per day.

Methadone is metabolized by demethylation (cytochrome P[450] 2D6 [CyP 2D6]) to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and to 2-ethyl-5-methyl-3,3-diphenylpyrrolidinr (EMDP). Individuals with genetic deficiencies of CyP 2D6 or coadministered amiodarone, paroxetine protease inhibitor antiretrovirals, chlorpheniramine, or other drugs that inhibit CyP 2D6 will accumulate methadone with associated toxicity.

Clinical

Methadone Confirmation, Urine
#83129

Useful For
Compliance monitoring of methadone therapy in patients being treated for heroin addiction

Interpretation
The urine output of methadone associated with minimal effective therapy is 1,000-50,000 ng/mL. Because only 5% is excreted unmetabolized, there is little correlation of urine concentration with dose.

Cautions
No significant cautionary statements

References
2. Baselt RC: Disposition of toxic drugs and chemicals in man. 5th edition. Foster City, CA, Chemical Toxicology Institute, 2000, pp 523-527

Method
Gas Chromatography-Mass Spectrometry (GC-MS). (Enger R: Modified from United Chemical Technologies, Inc., method entitled "Methadone in Urine For GC/MS Confirmations using: 200mg Clean Screen Extraction Column [ZSDAU020 or ZCDAU020]" [Unpublished Mayo information])

Specimen Required: 10 mL from a random urine collection. No preservative. Send specimen refrigerated in a 13-mL urine tube.

For situations where chain-of-custody is required, a chain-of-custody kit (Supply T282) is available. For chain-of-custody information, see #9426 “Chain-of-Custody Processing.”

NOTE: Additional drug panels and specific requests are available. Call Mayo Medical Laboratories at 800-533-1710.
Test Title: Methadone Confirmation, Urine
#83129

Reference Values: Positive
Typical Positive: 1,000-50,000 ng/mL
Cutoff concentrations:
  IMMUNOASSAY SCREEN: <300 ng/mL
  METHADONE, u-BY GC/MS: <100 ng/mL

Analytic Time: 2 days
Days Set Up: Monday through Friday
Fee: $97.20
CPT Code: 83840
Levetiracetam (Keppra) is approved for adjunctive therapy and treatment of partial onset seizures in adults with epilepsy. Levetiracetam is 100% bioavailable. Once absorbed, it is <10% bound to protein and has a volume of distribution of 1.0 L/kg. Following an oral dose, it reaches maximum concentration in 1 hour. The clearance half-life is 7 ± 1 hour and clearance is 0.96 mL/min/kg predominately by renal elimination of the parent drug. Twenty-four percent of the parent drug undergoes hepatic metabolism to an inactive carboxylic acid metabolite.

In adults, maximum blood concentration correlates with dose:

<table>
<thead>
<tr>
<th>Dose (b.i.d.)</th>
<th>C [Max] (µg/mL)</th>
<th>C [Min] (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg</td>
<td>10-25</td>
<td>3-10</td>
</tr>
<tr>
<td>1000 mg</td>
<td>23-40</td>
<td>5-37</td>
</tr>
<tr>
<td>1500 mg</td>
<td>36-63</td>
<td>7-34</td>
</tr>
</tbody>
</table>

Levetiracetam is cleared predominately by renal function. One can anticipate 40% reduction in levetiracetam clearance if the renal clearance is between 50-80 mL/min and 60% reduction in levetiracetam clearance if the creatinine clearance is <30 mL/min. Prepubescent children clear levetiracetam 40% faster than adults. There are no pharmacokinetic interactions between levetiracetam and other antiepileptic drugs.

Clinical

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Useful For

This test is used for monitoring levetiracetam therapy. Because levetiracetam has a wide therapeutic index and linear dose-concentration dependence, drug monitoring is not indicated in all patients. Drug concentration monitoring can be useful in documenting failure to respond that may be due to noncompliance, or to guide dosage adjustments in patients with renal failure.

Interpretation

The minimal effective serum concentration for seizure control is 3 µg/mL. Peak therapeutic serum concentrations of 10-63 µg/mL occur 1 hour after dose. Trough therapeutic concentrations occurring just before the next dose range from 3-34 µg/mL.

Toxicity known to be associated with levetiracetam use includes decreased RBC count and hematocrit, decreased neutrophil count, somnolence, asthenia, and dizziness. These toxicities may be associated with blood concentrations in the therapeutic range.

Cautions

Coadministration of cimetidine will interfere with the test, producing artifactualy increased measurements of levetiracetam. The presence of cimetidine can be identified by the laboratory and laboratory reports will reflect cimetidine interference if it is detected.

References

Test Title: Levetiracetam, Serum
#83140

Method
Serum is mixed with internal standard. The drug is extracted into methylene chloride at a neutral pH. The organic layer is transferred and evaporated. The specimen is reconstituted and analyzed by HPLC with 2 wavelengths to identify interferences. (Ratnaraj N, Doheny H, Patsalos P: A micromethod for the determination of the new antiepileptic drug levetiracetam in serum or plasma by high performance liquid chromatography. Therapeutic Drug Monitoring 1996;18:154-157)

Specimen Required: Draw blood in a plain red-top tube(s). Spin down and send 0.5 mL of serum ambient.

Reference Values: Peak concentration: 10-63 µg/mL
Trough concentration: 3-34 µg/mL

Analytic Time: 1 day
Days Set Up: Monday through Saturday
Fee: $79.50
CPT Code: 82491
Human papillomaviruses (HPV) are composed of an icosahedral viral particle (virion) containing an 8000 base pair double-stranded circular DNA molecule surrounded by a protein capsid.

HPV infections are sexually transmitted. The presence of HPV in the female genital tract is associated with a number of disease states including genital condyloma acuminata; condyloma plana; Bowenoid papulosis; and cervical, vaginal, and vulvar intraepithelial neoplasia and carcinoma.

Numerous types of HPV viruses have been identified by molecular analysis. These HPV types also can be categorized into low, intermediate, and high-risk groups based on their relative distribution in various histopathological diagnosis categories. Detection of high-risk genotypes (n=13) from genital specimens is considered a major determinant associated with the development of cervical cancer. Historically, HPV 16 and HPV 18 have been regarded as high-risk cancer-associated HPVs; HPV types 6 and 11 as low risk; and HPV types 31, 33, and 35 have been demonstrated to have an intermediate association with cancer. Despite this useful conceptual framework, these 7 HPV types have been found in only about 70% of cervical neoplasms. Additional HPVs, including types 42, 43, 44, 45, 51, 52, 56, 58, 59, and 68, have been identified as the principal HPVs detected in the remaining lesions. HPV DNA also is present in approximately 10% of women with normal cervical epithelium, but the actual prevalence is strongly influenced by age and other demographic variables.

Prospective studies have shown that 15-28% of HPV DNA-positive women developed squamous intraepithelial neoplasia within 2 years, compared with only 1-3% of HPV DNA-negative women. In particular, the risk of progression for HPV types 16 and 18 was greater (approximately 40%) than for other HPV types.

For patients with "atypical squamous cells of unknown significance" (ASCUS) on Pap smear, HPV typing may be used to determine the need for colposcopy. Patients who are positive for a high-risk HPV type may be referred to colposcopy; patients who are negative may be followed according to the usual clinical practice.

While certain HPV types are strongly associated with cervical cancer, there is clear evidence that cofactors are involved. The nature and roles of these cofactors are under intense study; however, their contributions to malignant progression are still poorly understood. Some of the cofactors thought to interact with cancer-associated HPV types in the genesis of cervical malignancy are the herpes viruses, tobacco products, oral contraceptives, and certain dietary factors.

**Useful For**

- Detection of high-risk genotypes associated with the development of cervical cancer
- As an aid to triaging women with abnormal Pap smear results
Human Papillomavirus (HPV) Detection-High Risk Types

#83344

**Test Title:**

A positive result indicates the presence of HPV DNA due to 1 or more of the following genotypes of the virus: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. A negative result indicates the absence of HPV DNA of the target genotypes.

For patients with atypical squamous cells of unknown significance (ASCUS) Pap smear results and positive for high-risk HPV types, consider referral to colposcopy if clinically indicated. (5-7)

**Interpretation**

- This test is not recommended for evaluation of suspected sexual abuse.
- The prevalence of HPV infection in a population may affect performance; positive predictive values decrease in populations with high prevalence of individuals with low risk of infection.
- A negative result does not exclude the possibility of HPV infection (eg, sampling errors may cause false-negative results).
- If high concentrations of antifungal cream, contraceptive jelly, or douche are present when the specimen is collected, false-negative results may be obtained, especially if the specimen contains HPV DNA levels near the assay cutoff.
- This test can only be used with cervical specimens collected using the Digene Cervical Sampler of Digene Specimen Transport Medium or cervical specimens collected using a broom-type collection device and placed in Cytic ThinPrep Pap Test PreservCyt Solution. Biopsy specimens may be assayed only if they are placed immediately in Digene Specimen Transport Medium and stored at -20°C until assayed.
- Cross-reactivity between both HC2 HPV DNA test probes and the bacterial plasmid pBR322 is possible and the presence of pBR322 homologous sequences has been reported in human genital specimens. False-positive results could occur in the presence of high levels of bacterial plasmid.

**Cautions**

**Supportive Data**

Comparison of HC2 HPV DNA Test versus ASCUS (referral Pap population, Kaiser)

<table>
<thead>
<tr>
<th></th>
<th>HSIL or greater of the time of colposcopy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td>High-risk HPV probe</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>317</td>
</tr>
<tr>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>497</td>
</tr>
</tbody>
</table>

Among patients presenting with an ASCUS referral Pap smear, the negative predictive value of the HC2 HPV DNA test for having HSIL or greater disease of colposcopy is 99.0%. Sensitivity = 93.0% (66/71).

**References**

Method

The Digene Hybrid Capture II System (HC2) is a qualitative HPV test that identifies the presence of most high-risk types of the virus (16/18/31/33/35/39/45/51/52/56/58/59/68). HC2 is a sandwich capture, molecular hybridization assay with signal amplification that utilizes chemiluminescent detection and is performed in microplate wells. Specimens containing the target DNA hybridize with a specific HPV RNA probe cocktail. The resultant RNA:DNA hybrid is captured onto the surface of a microplate well coated with antibodies specific for RNA:DNA hybrids. Immobilized hybrids are then reacted with antihybrid antibodies conjugated to alkaline phosphatase and detected with a chemiluminescent substrate. As the substrate is cleaved by the bound alkaline phosphatase, light is emitted, which is measured as relative light units (RLUs) on a luminometer. The intensity of the light is proportional to the amount of target DNA in the specimen. (Package insert: Digene HPV Test Hybrid Capture® II. Digene Corp, Beltsville, MD 2002)

Specimen Required: SUBMIT ONLY 1 OF THE FOLLOWING SPECIMENS:

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Container Type</th>
<th>Description</th>
<th>Preferred Transport Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical biopsy</td>
<td>Digene specimen transport medium</td>
<td>3-5 mm in diameter cervical biopsy placed immediately into 1.0 mL Digene transport medium.</td>
<td>Frozen</td>
</tr>
<tr>
<td>Cervical or endocervical swab</td>
<td>Digene specimen transport medium</td>
<td>Collect cervical specimen on swab, swirl swab in transport medium and screw cap on tightly.</td>
<td>Refrigerate</td>
</tr>
<tr>
<td>Cervical or endocervical swab</td>
<td>Cytoc PreservCyt Solution (Thin-Prep vial must contain at least 4.0 mL PreservCyt solution)</td>
<td>Collect cervical specimen on swab, swirl swab in transport medium and screw cap on tightly.</td>
<td>Ambient</td>
</tr>
</tbody>
</table>

Reference Values: Negative for types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68

Analytic Time: 2 days

Days Set Up: Monday through Saturday

Fee: $113.70

CPT Code: 87621