Several antineuronal autoantibodies are clinically recognized as markers of a patient’s immune response to (paraneoplastic autoantibodies) specific cancers. Seropositive patients present with neurologic symptoms and signs in >90% of cases. The cancers are most commonly small-cell lung carcinoma (SCLC), ovarian (or related mullerian) carcinoma, breast carcinoma, thymoma, or Hodgkin’s lymphoma. The cancers may be new or recurrent, are usually limited in metastatic volume, and are often occult by standard imaging procedures.

Detection of the appropriate autoantibodies allows early diagnosis and treatment of the cancer, which may lessen neurological morbidity and improve survival.

Serum is the preferred specimen for paraneoplastic autoantibodies. However, cerebrospinal fluid (CSF) results are sometimes positive when serum results are negative. Additionally, CSF is more readily interpretable because it generally lacks the interfering non-organ-specific antibodies that are common in serum of patients with cancer. Because the neurologists typically perform spinal taps in these patients, serum and CSF testing are recommended to improve the detection rate.

### Paraneoplastic Autoantibody Evaluation, Spinal Fluid #80013

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### Clinical Information

Several antineuronal autoantibodies are clinically recognized as markers of a patient’s immune response to (paraneoplastic autoantibodies) specific cancers. Seropositive patients present with neurologic symptoms and signs in >90% of cases. The cancers are most commonly small-cell lung carcinoma (SCLC), ovarian (or related mullerian) carcinoma, breast carcinoma, thymoma, or Hodgkin’s lymphoma. The cancers may be new or recurrent, are usually limited in metastatic volume, and are often occult by standard imaging procedures.

Detection of the appropriate autoantibodies allows early diagnosis and treatment of the cancer, which may lessen neurological morbidity and improve survival.

Serum is the preferred specimen for paraneoplastic autoantibodies. However, cerebrospinal fluid (CSF) results are sometimes positive when serum results are negative. Additionally, CSF is more readily interpretable because it generally lacks the interfering non-organ-specific antibodies that are common in serum of patients with cancer. Because the neurologists typically perform spinal taps in these patients, serum and CSF testing are recommended to improve the detection rate.

### Useful For

- As an aid in the diagnosis of paraneoplastic neurological autoimmune disorders related to carcinoma of lung, breast, ovary, thymoma or Hodgkin’s lymphoma.
- In patients with a history of tobacco use or other lung cancer risk, or if thymoma is suspected, #81256 “Paraneoplastic Autoantibody Lung/Thymoma Panel, Serum” is also recommended.

### Interpretation

**Anti-Neuronal Nuclear Antibody-Type 1 (ANNA-1 or anti-Hu)**

In adults, this antibody is found almost exclusively in patients with a history of tobacco use or passive exposure.

Cancer has been found in >90% of seropositive patients identified as seropositive for ANNA-1 by Mayo Clinic’s Neuroimmunology Laboratory (n=540; female: male=2:1). SCLC has been found in 83% of patients. A second malignant neoplasm is found in 13% of patients positive for ANNA-1 who have SCLC. Therefore, the search for SCLC should not stop if a non-SCLC tumor is found. ANNA-1 is also a rare accompaniment of thymoma.

The most common presentation of patients seropositive for ANNA-1 is peripheral neuropathy (sensory > sensorimotor > autonomic >> motor), but they can exhibit any element of an encephalomyelo-radiculoopathy; 12% present with gastrointestinal dysmotility (gastroparesis, pseudo-obstruction, esophageal achalasia, pyloric stenosis, or anal spasm).

ANNA-1 has been identified in children with acquired cerebellar ataxia, encephalopathy, or intestinal pseudoobstruction. Peripheral neuroblastomas are sometimes identifiable.
Anti-Neuronal Nuclear Antibody-Type 2 (ANNA-2 or anti-Ri)
ANNA-2 is a rare paraneoplastic autoantibody. It is a marker of breast carcinoma and SCLC. It has been reported most often in postmenopausal women. In Mayo Clinic Neuroimmunology Laboratory’s prospective experience, 8 of 30 ANNA-2 positive patients have been male.

Seropositive patients often present with signs of midbrain, brain stem, cerebellar, or spinal cord dysfunction. Ocular opsoclonus-myoclonus or jaw spasm may be prominent. Sensorimotor neuropathy is sometimes seen.

Of 28 patients identified in Mayo Clinic’s Neuroimmunology Laboratory as seropositive for ANNA-2, and followed up clinically, 24 had evidence of active cancer: histologically proven lung carcinoma (10), chest imaging abnormality consistent with lung cancer (3), histologically proven breast carcinoma (n=9), recurrent uterine cervical carcinoma (n=1) and bladder carcinoma. Continued surveillance increased the cancer detection frequency. A majority improved neurologically after immunomodulatory or tumor-directed therapy.

For patients with a clinically unexplained neurologic disorder, detection of ANNA-2 in serum or CSF identifies the neurologic problem as autoimmune and almost certainly paraneoplastic, targets the search for underlying malignancy (breast, lung, or gynecologic), leads to early treatment of cancer, and consideration of immunosuppressant therapy.

Treatment of the cancer associated with ANNA-2 can lead to stabilization and even striking improvement of the neurologic disorder and progressive reduction of the autoantibody titer.

Anti-Neuronal Nuclear Antibody-Type 3 (ANNA-3)
A positive result confirms that a patient’s subacute neurological disorder has an autoimmune basis and has a 90% predictive value for an aerodigestive carcinoma, usually SCLC, that is new or recurrent and confined to the chest.

Fifteen percent of patients who are eventually proven to have small-cell carcinoma have an unrelated, often more obvious cancer, either coexisting or in the past.

ANNA-3 has not yet been encountered in patients with lung carcinoma without a neurological accompaniment (n=100), or with other cancers (n=300), or in healthy subjects (n=100).

Purkinje Cell Cytoplasmic Antibody-Type 1 (PCA-1 or anti-Yo)
This antibody is found almost exclusively in women (<1% men) and is a marker of an immune response initiated by ovarian carcinoma, a related mullerian neoplasm, or breast carcinoma.

Seropositive patients usually present with a prominent subacute cerebellar ataxia with variable elements of encephalomyeloradiculopatulay. In Mayo Clinic Neuroimmunology Laboratory’s prospective experience with 260 patients seropositive for PCA-1: a carcinoma was found in 90% of seropositive patients (ovarian or other mullerian or breast); >90% of patients presented with cerebellar ataxia; 5% presented with sensorimotor or motor neuropathy, and of these all had a pelvic neoplasm consistent with mullerian carcinoma.

PCA-1 antibody has not been found in any healthy subject. It is rarely found in patients with neurologic diseases (including cerebellar disorders) without gynecologic or breast cancer. The ovarian cancers are typically limited in metastatic spread and may not be detected by imaging procedures. If mammography is negative, regardless of CA125 elevation, exploratory laparotomy is advisable (as for a “second look” in management of ovarian carcinoma). Breast carcinoma may coexist with a mullerian cancer. PCA-1 antibody is rarely found in patients with gynecologic cancer without neurologic dysfunction (<2%).

Purkinje Cell Cytoplasmic Antibody-Type 2 (PCA-2)
A positive value (at 1:2 dilution or higher) is consistent with neurological autoimmunity, and justifies a thorough search for a lung cancer, particularly small-cell carcinoma. The cancers are usually limited in metastasis. An extra-pulmonary primary small-cell carcinoma (eg, skin, breast, larynx, cervix, prostate) should be considered.

PCA-2 is found in <2% of patients with uncomplicated SCLC.
Interpretation

**Purkinje Cell Cytoplasmic Antibody Tr (PCA-Tr)**
A positive value (at 1:2 dilution or higher) is consistent with neurological autoimmunity and justifies a search for Hodgkin’s lymphoma. PCA-Tr has not yet been identified in any other context.

Seropositive patients usually have Hodgkin’s lymphoma and present with subacute cerebellar ataxia.

**Amphiphysin**
A positive result is consistent with neurologic autoimmunity, usually related to breast carcinoma or SCLC.

**Paraneoplastic Autoantibody Western Blot Confirmation**
A positive result confirms that a patient’s subacute neurological disorder has an autoimmune basis and has 80-90% predictive value for a definable neoplasm. Seropositivity is sometimes found in patients who have limited cancer metastasis without evidence of neurological autoimmunity, especially small-cell carcinoma.

These IgG serologic markers of paraneoplastic neurologic autoimmunity are not detected in serum or cerebrospinal fluid (CSF) of healthy individuals and are very infrequent in patients who have cancer without evidence of neurologic dysfunction.

Novel neuron-restricted autoantibodies, as yet unclassified, are sometimes recognizable as tumor-associated. Follow-up of several patients of this type indicates that some of these unclassified autoantibodies are associated with small cell, ovarian, and breast carcinomas.

**CRMP-5-IgG**
Detection of IgG autoantibody specific for the neuronal cytoplasmic antigen CRMP-5 in a patient’s serum or CSF confirms that the patient’s subacute neurological disorder has an autoimmune basis and has 75-80% predictive value for SCLC or thymoma.1

CRMP-5-IgG titers generally fall after the neoplasm is treated, and a rising titer is indicative of tumor persistence or recurrence.

Cautions

- PCA-1 is rarely found in male patients (<1%) and not in Mayo Clinic’s experience in paraneoplastic cerebellar degeneration associated with lung cancer.
- Not recommended as a general screening test for cancer.
- Seronegativity does not exclude malignancy.

References
2. Lucchinetti CF, Kimmel DW, Lennon VA: Paraneoplastic and oncological profiles of patients seropositive for type 1 anti-neuronal nuclear antibody. Neurology 1998;50:652-657

Method

Indirect Immunofluorescence Assay (IFA)
The patient’s serum or CSF is tested by a standardized IFA that uses a composite frozen section of mouse cerebellum, kidney, and gut tissues. After incubation with serum or CSF and washing, fluorescein-conjugated goat antihuman IgG is applied. Neuron-specific autoantibodies are identified by their characteristic fluorescence staining patterns. Antibody of ANNA-1 specificity is panneuronal in reactivity; it binds to the cytoplasm and nucleus (sparing nucleolus) of central and peripheral nervous system neurons. Antibody of ANNA-2 specificity has a similar binding pattern but reactivity is restricted to neurons of the central nervous system; neurons of the peripheral nervous system are nonreactive. Antibody of PCA-1 specificity bind distinctively to endoplasmic reticulum in Purkinje
cells, molecular neurons, and other large neurons in the central and peripheral nervous system. Sera and CSF that are scored positive for any neuronal nuclear or cytoplasmic autoantibody are titrated to an endpoint on mouse Purkinje cells or peripheral neurons. Interference by coexisting non-neuronal-specific autoantibodies can usually be eliminated by serologic absorption. Occasionally Western blot analysis is required. (Yu Z, Kryzer TJ, Griesmann GE, Kim K-K, et al: CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. Ann Neurol 2001;49:146-154)

Western Blot
Western blot testing is indicated in the infrequent situation that interference by coexisting non-neuronal-specific autoantibodies precludes IFA interpretation. It is not cost effective for routine serologic screening. However, results obtained by Western blot analyses in Mayo Clinic’s Neuroimmunology Laboratory have shown 100% concordance with IFA results for PCA-1 and superior sensitivity of the IFA for deletion of ANNA-1 and ANNA-2. An aqueous extract of adult rat cerebellar proteins is used as the source of neuronal antigens. Western blot is performed on denatured and reduced proteins separated by electrophoresis on 10% polyacrylamide gel. (Vernino S, Lennon VA: New Purkinje cell antibody (PCA-2): marker of lung cancer-related neurological autoimmunity. Ann Neurol 2000 March;47(3):297-305)

Specimen Required: 4.0 mL of spinal fluid. Send specimen refrigerated.

NOTE: Include name, phone number, mailing address, and E-mail address (if applicable) of ordering physician.

Reference Values:
- **ANTI-NEURONAL NUCLEAR ANTIBODY- Type 1 (ANNA-1)**
  - Negative at <1:2
- **ANTI-NEURONAL NUCLEAR ANTIBODY- Type 2 (ANNA-2)**
  - Negative at <1:2
- **ANTI-NEURONAL NUCLEAR ANTIBODY- Type 3 (ANNA-3)**
  - Negative at <1:2
- **PURKINJE CELL CYTOPLASMIC ANTIBODY, Type 1 (PCA-1)**
  - Negative at <1:2
- **PURKINJE CELL CYTOPLASMIC ANTIBODY, Type 2 (PCA-2)**
  - Negative at <1:2
- **PURKINJE CELL CYTOPLASMIC ANTIBODY, Type Tr (PCA-Tr)**
  - Negative at <1:2
- **AMPHIPHYSPIN**
  - Negative at <1:2
- **CRMP-5-IgG**
  - Negative at <1:2
- **PARANEOPLASTIC AUTOANTIBODY WESTERN BLOT CONFIRMATION**
  - Negative (reported as positive or negative)

Analytic Time: 3 days if neg/5 days if pos
Days Set Up:
- **ANNA-1:** Monday through Friday
- **ANNA-2:** Monday through Friday
- **ANNA-3:** Monday through Friday
- **PCA-1:** Monday through Friday
- **PCA-2:** Monday through Friday
- **PCA-Tr:** Monday through Friday
- **Amphiphysin:** Monday through Friday
- **CRMP-5-IgG:** Monday through Friday
- **Paraneoplastic autoantibody Western blot confirmation:** Tuesday, Thursday

Fee: $539.30
CPT Code: 86256/x8 Amphiphysin, ANNA-1, ANNA-2, ANNA-3, CRMP-5-IgG, PCA-1, PCA-2, and PCA-Tr
84182/Paraneoplastic autoantibody Western blot confirmation (if appropriate)
Astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas are the major histologic types of human gliomas; histologic differentiation among these tumors can be difficult. Recently, it has been shown that specific genetic alterations are highly associated with specific morphologic types of gliomas. In addition, specific genetic alterations seem to predict prognosis (survival) as well as response to specific chemotherapeutic and radiotherapeutic regimens, irrespective of tumor morphology.

- Deletions of the short arm and long arm of chromosomes 1 (1p) and 19 (19q), respectively, are strongly correlated with gliomas of oligodendroglial morphology. Approximately 70%, 50%, and 50% of oligodendrogliomas have deletions of 19q, 1p, and of both 19q and 1p, respectively.
- Combined 1p and 19q loss is infrequent in gliomas of astrocytic origin. Thus, the presence of combined 1p/19q loss is strongly suggestive that a glioma is of oligodendroglioma lineage.
- Gains of chromosome 19 and of the 19 q-arm are associated with gliomas of astrocytic origin.
- Deletions of 1p and of both 1p and 19q have also been associated with response to various chemotherapeutic and radiotherapeutic regimens. These responses have been especially associated with high-grade oligodendrogliomas (anaplastic oligodendrogliomas).

**Fluorescence In Situ Hybridization (FISH) for 1p/19q Deletion in Gliomas #80029**

**Clinical**
Astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas are the major histologic types of human gliomas; histologic differentiation among these tumors can be difficult. Recently, it has been shown that specific genetic alterations are highly associated with specific morphologic types of gliomas. In addition, specific genetic alterations seem to predict prognosis (survival) as well as response to specific chemotherapeutic and radiotherapeutic regimens, irrespective of tumor morphology.

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- Combined 1p and 19q loss is infrequent in gliomas of astrocytic origin. Thus, the presence of combined 1p/19q loss is strongly suggestive that a glioma is of oligodendroglioma lineage.
- Gains of chromosome 19 and of the 19 q-arm are associated with gliomas of astrocytic origin.
- Deletions of 1p and of both 1p and 19q have also been associated with response to various chemotherapeutic and radiotherapeutic regimens. These responses have been especially associated with high-grade oligodendrogliomas (anaplastic oligodendrogliomas).

**Useful For**
- Predicting response of an oligodendroglioma to therapy
- The test is indicated when a diagnosis of oligodendroglioma, both low-grade (WHO, grade II) and anaplastic (WHO, grade III) is rendered. The test is also strongly recommended in mixed oligoastrocytomas.
- The test may be useful in tumors with a complex “hybrid” morphology requiring differentiation from pure astrocytomas, to support the presence of oligodendroglial differentiation/lineage.

**Interpretation**
- A tumor is considered to have 1p or 19q deletion when the 1p probe to 1q probe ratio (1p/1q) or the 19q probe to 19p probe ratio (19q/19p) is <0.80.
- A tumor is considered to have 19q gain when the 19q/19p ratio is >1.30.
- A tumor is considered to have chromosome 1 or 19 gain when the percentage of nuclei with ≥3 signals is >20%.
- The presence of 1p deletion and combined 1p and 19q deletion in oligodendrogliomas may indicate that the patient may respond to chemotherapy and radiation therapy.

**Cautions**
- The absence of 1p and 19q deletion does not exclude the diagnosis of oligodendroglioma.
- The absence of chromosome 19 gain does not exclude the diagnosis of high-grade astrocytoma (glioblastoma multiforme).
- This method is designed for formalin-fixed, paraffin-embedded tissue. Other methods of fixation, especially those that contain ethanol, use a low pH, or contain heavy metal ions (eg, Bouin’s and “Prefer”) may interfere with FISH.
- Only specimens that contain identifiable tumor tissue can be analyzed.
- The FISH results should be interpreted in conjunction with clinical and pathologic findings.
The normal reference range for 1p/1q and 19q/19p was established using several normal value studies.

Table 1 summarizes the incidence of 1p deletion, 19q deletion, and combined 1p and 19q deletion in a series of tumors from Mayo Clinic and Johns Hopkins University. The laboratory has also detected a similar incidence of 1p and 19q deletions in a series of 189 high-grade oligodendrogliomas from patients enrolled in a Radiation Therapy Oncology Group (RTOG) trial.

### Table 1: Incidence of 1p and 19q Losses Versus Glioma Subtype and Primary Status

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*Specimens derived from initial surgical resection.
†Specimens derived from noninitial surgical resection.

### Supporting Data

The normal reference range for 1p/1q and 19q/19p was established using several normal value studies. Table 1 summarizes the incidence of 1p deletion, 19q deletion, and combined 1p and 19q deletion in a series of tumors from Mayo Clinic and Johns Hopkins University. The laboratory has also detected a similar incidence of 1p and 19q deletions in a series of 189 high-grade oligodendrogliomas from patients enrolled in a Radiation Therapy Oncology Group (RTOG) trial.

### References

Fluorescence In Situ Hybridization (FISH) for 1p/19q Deletion in Gliomas

Test Title:

Reference Values:

Analytic Time:

Fee:

CPT Code:

Specimen Required:

Method

FISH with locus-specific probes to the minimally deleted regions of 1p (1p36) and 19q (19q13.3) is used to detect 1p and 19q deletion. Two dual-probe FISH hybridizations are performed: a 1p36 probe (labeled with a red fluorophore) is combined with a control 1q probe (labeled with a green fluorophore). Similarly, a 19q13.3 probe is combined with a control 19p probe. The hybridization assay has been optimized to detect 1p deletion and 19q deletion in paraffin-embedded tumor specimens. The assay also will detect chromosome 1 and 19 gain, as well as 19 q-arm gain.

The assay is performed on 5-μm paraffin sections. A parallel H&E stained section is examined by a Mayo Clinic pathologist to determine where tumor is located within the specimen. Unstained sections are processed in the Cytogenetics Laboratory using standard FISH procedures for paraffin-embedded tissue. The loci tested are 1p36 (p73), 1q24 (HPC1), 19p13 (D19S221), and 19q13.3 (EDH2). A total of 60 metaphase nuclei (2 scorers, 30 each) within the previously identified tumor lesions are scored. If there are fewer than 60 nuclei within the lesion, as few as 20 cells may be scored by each scorer. Results are expressed as a ratio to determine the deletion status of the specimen. (Smith JS, Perry A, Borell TJ, et al: Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas. J Clin Oncol 2000 February;18(3):636-645)

References

(continued)


Specimen Required:

Formalin-fixed, paraffin-embedded tumor tissue block.
Include 1 hematoxylin-and-eosin stained slide.
NOTE: Please complete a “Hematopathology/Molecular Oncology/Cytogenetics Request Form” (Supply T241), or a “MayoConnect Additional Test Information” form (Supply T357) and forward it with the specimen.

Reference Values:

1p/1q ratio: 0.90-1.05
19q/19p ratio: 0.93-1.02

Analytic Time:

3-5 days

Days Set Up:

Monday through Sunday

Fee:

$669.00

CPT Code:

88271/x4 DNA probe, each
88275/x2 Interphase in situ hybridization
88313/Stain
88365/Interpretation and report
Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is a hypothalamic polypeptide that is transported along the axons of the synthesizing neurons into the posterior pituitary gland. From there it is released into the systemic circulation after appropriate stimuli. The main regulators of AVP secretion are osmotic stimuli, provided by osmoreceptors located in the anteromedial hypothalamus, and volume stimuli provided by receptors in neck vessels and heart. Under physiological conditions, volume stimuli always override osmotic stimuli.

The absence or presence of AVP is the major physiologic determinant of urinary free water excretion or retention. AVP acts principally on renal collecting tubules to increase water reabsorption. The antidiuretic effects of AVP are mediated by V2 vasopressin receptors. AVP can also increase vascular resistance through stimulation of V1 receptors.

Diabetes insipidus (DI) is characterized by the inability to appropriately concentrate urine in response to volume and osmol stimuli. The main causes for DI are decreased AVP production (central DI) or decreased renal response to AVP (nephrogenic DI).

Clinical

Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is a hypothalamic polypeptide that is transported along the axons of the synthesizing neurons into the posterior pituitary gland. From there it is released into the systemic circulation after appropriate stimuli. The main regulators of AVP secretion are osmotic stimuli, provided by osmoreceptors located in the anteromedial hypothalamus, and volume stimuli provided by receptors in neck vessels and heart. Under physiological conditions, volume stimuli always override osmotic stimuli.

The absence or presence of AVP is the major physiologic determinant of urinary free water excretion or retention. AVP acts principally on renal collecting tubules to increase water reabsorption. The antidiuretic effects of AVP are mediated by V2 vasopressin receptors. AVP can also increase vascular resistance through stimulation of V1 receptors.

Diabetes insipidus (DI) is characterized by the inability to appropriately concentrate urine in response to volume and osmol stimuli. The main causes for DI are decreased AVP production (central DI) or decreased renal response to AVP (nephrogenic DI).

Useful For

• Diagnosis and characterization of diabetes insipidus (DI)
• Diagnosis of psychogenic water intoxication and ectopic AVP production, particularly due to bronchogenic carcinoma
• As an adjunct in the diagnosis of inappropriate ADH syndrome (SIADH), which results in dilutional hyponatremia

Interpretation

Central DI can be differentiated from nephrogenic DI by measuring AVP during a state of maximal, or near maximal, stimulus for AVP release (water deprivation test; plasma osmolality >295 mOsm/kg water and/or >5% loss in body weight) and assessing the antidiuretic response to exogenous administration of the AVP at the conclusion of a water deprivation test:

- If AVP is low despite elevated serum osmolality, and the urine osmolality increases significantly after exogenous AVP, the diagnosis is compatible with central DI.
- If stimulated AVP is elevated and the administration of exogenous AVP results in little or no increase in urine concentration, the patient likely has nephrogenic DI.
- Mixed forms of DI can exist and both central and peripheral DI may be incomplete, complicating interpretation. In addition, prolonged psychogenic polydipsia can lead to a loss of concentrating gradient across the nephron, simulating nephrogenic DI.

An elevated plasma AVP level in a hyponatremic, euvoletic patient may be indicative of SIADH. In hypovolemic patients, it represents a physiological response to hypovolemia.

Seizures, cerebral hemorrhages, neurosurgery, and electroconvulsive therapy can all result in short-lived artefactual AVP elevations.
Cautions

- Reference values were determined on platelet-poor EDTA plasma from individuals fasting no longer than overnight. A significant amount of circulating AVP is associated with platelets. Therefore, various conditions affecting platelets may also affect AVP levels. Platelet-rich specimens have been shown to have AVP levels on the order of 10 times the value of platelet-poor specimens.
- AVP levels obtained in the process of a water deprivation test may be difficult to interpret because of the many nonstandardized variables in this test. Expert consultation is recommended in these circumstances.

References


Method

This method uses a cartridge extraction of acidified plasma to prepare the specimen for an in-house radioimmunoassay (RIA). After acidification, the specimen is centrifuged, applied to a phenyl cartridge, washed, and eluted. The extract is dried under nitrogen, reconstituted with assay buffer and measured for AVP by RIA. (Skowsky WR, Rosenbloom AA, Fisher DA: Radioimmunoassay measurement of arginine vasopressin in serum: development and application. J Clin Endocrinol Metab 1974 February;38(2):278-287)

Specimen Required:

1. Have patient fast and thirst for 6 hours.
   
   **NOTE: No liquids, including water, are allowed.**

2. Draw blood in a lavender-top (EDTA) tube(s), and process 5.0 mL of EDTA whole blood as follows:
   A. Spin down in a refrigerated centrifuge at approximately 1,000 x G (2,000 rpm for a 20 cm radius centrifuge) for 10 minutes.
   B. Remove plasma, carefully avoiding the platelet/buffy coat.

3. Send 2.0 mL of EDTA platelet-poor plasma frozen in plastic vial. (Glass vials cannot be accepted.)

Reference Values:

Adults: <1.7 pg/mL

Reference values were determined on platelet-poor EDTA plasma from individuals fasting no longer than overnight.

Analytic Time: 3 days

Days Set Up: Tuesday

Fee: $86.90

CPT Code: 84588
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 of time, 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 (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 of time, 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.

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Useful For

• Compliance monitoring of methadone therapy in patients being treated for heroin addiction
• Assessing toxicity

Interpretation

The minimal effective serum concentration for analgesia is 30 ng/mL. Peak therapeutic serum concentrations of 30-90 ng/mL occur 4 hours after dose. Patients continuously administered methadone develop tolerance and have higher serum concentrations than indicated by the reference range; these patients may tolerate concentrations up to 400 ng/mL. Methadone concentrates in serum; the ratio of blood to serum methadone is 0.75.

Cautions

Because methadone has a wide therapeutic index and dose-dependent toxicity, routine drug monitoring is not indicated in all patients.

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: 200 mg Clean Screen Extraction Column [ZSDAU020 or ZCDAU020]” [Unpublished Mayo information])
<table>
<thead>
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**Specimen Required:**
Draw blood in a plain red-top tube(s). Spin down and send 3.0 mL of serum refrigerated.

<table>
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<td>Analytic Time: 1 day</td>
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