MAYO CLINIC LABORATORIES

Test Definition: PNYG

Phenytoin, Total and Phenobarbital Group, Serum

Overview

Useful For

Monitoring for appropriate therapeutic concentration of phenytoin and phenobarbital

Assessing compliance or toxicity

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
PNYA	Phenytoin, Total, S	Yes	Yes
PBR	Phenobarbital, S	Yes	Yes

Method Name

Kinetic Interaction of Microparticles in a Solution (KIMS)

NY State Available

Yes

Specimen

Specimen Type

Serum
Serum Red

Specimen Required

One serum specimen (0.5 mL of serum) may be sent if using a red top tube.

Serum for Phenytoin:
Collection Container/Tube: Red top
Submission Container/Tube: Plastic vial
Specimen Volume: 0.5 mL
Collection Instructions: Centrifuge and aliquot serum into a plastic vial within 2 hours of collection.

Serum for Phenobarbital:
Container/Tube:
Preferred: Serum gel
Acceptable: Red top
Submission Container/Tube: Plastic vial
Specimen Volume: 0.5 mL

Collection Instructions:

1. Serum gel tubes should be centrifuged within 2 hours of collection.
2. Red-top tubes should be centrifuged, and the serum aliquoted into a plastic vial within 2 hours of collection.

Forms

If not ordering electronically, complete, print, and send a Therapeutics Test Request (T831) with the specimen.

Specimen Minimum Volume

0.25 mL for 2 specimens; 0.25 mL for 1 serum red top

Reject Due To

Gross hemolysis	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Ambient	72 hours	
	Refrigerated (preferred)	14 days	
	Frozen	28 days	
Serum Red	Ambient	7 days	
	Refrigerated (preferred)	7 days	
	Frozen	14 days	

Clinical & Interpretive

Clinical Information

Phenytoin, Total:
Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective.

Initial therapy with phenytoin is started at doses of 100 to 300 mg/day for adults or 4 mg/kg/day for children. Because absorption is variable and the drug exhibits zero-order (nonlinear) kinetics, dose must be adjusted within 5 days using blood concentration to guide therapy. Oral bioavailability ranges from 80% to 95% and is diet-dependent.

Phenytoin exhibits zero-order pharmacokinetics; the rate of clearance of the drug is dependent upon the concentration of drug present. Therefore, phenytoin does not have a classical half-life like other drugs, since it varies with blood concentration. At a blood concentration of 15 mcg/mL, approximately half the drug in the patient's body will be eliminated in 20 hours. As the blood concentration drops, the rate at which phenytoin is excreted increases.

Phenytoin has a volume of distribution of 0.65 L/kg, and is highly protein bound (90%), mostly to albumin. Some drug side-effects occur in the therapeutic range; these include gingival hyperplasia, hyperglycemia, and skin rash.

Phenytoin pharmacokinetics are significantly affected by a number of other drugs. As noted above, phenytoin and phenobarbital are frequently coadministered. Induction of the cytochrome P450 enzyme system by phenobarbital will increase the rate at which phenytoin is metabolized and cleared. At steady-state, enzyme induction will increase the rate of clearance of phenytoin such that the dose must be increased approximately 30% to maintain therapeutic levels.

Uremia has a similar effect on phenytoin protein binding. In uremia, by-products of normal metabolism accumulate and bind to albumin, displacing phenytoin which causes an increase in the free fraction.

Valproic acid, an antiepileptic frequently coadministered with phenytoin, competes for the same binding sites on albumin as phenytoin. Valproic acid displaces phenytoin from albumin, reducing the bound fraction and increasing the free fraction. The overall effect of coadministration of a therapeutic dose of valproic acid is that the total concentration of phenytoin decreases due to increased clearance but the free fraction increases; the free concentration of phenytoin, which is the active form remains virtually the same. Thus, no dosage adjustment is needed when valproic acid is added to maintain the same pharmacologic effect, but the total concentration of phenytoin decreases.

In contrast to the valproic acid situation, in renal failure, there is not the same opportunity for the free phenytoin fraction to be cleared. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity.

The free phenytoin level is the best indicator of adequate therapy in renal failure.

Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity occurs when the blood concentration is >30 mcg/mL and is typified by tremor, hyperreflexia, and lethargy. The outcome of phenytoin toxicity is not as serious as phenobarbital because phenytoin is not a central nervous system sedative.

Phenobarbital:
Phenobarbital is a general central nervous system (CNS) suppressant that has proven effective in the control of generalized and partial seizures. It is frequently coadministered with phenytoin for control of complex seizure disorders and with valproic acid for complex parietal seizures.

Phenobarbital is administered in doses of 60 to 300 mg/day in adults or 3 to 6 mg/kg/day in children.

Phenobarbital is slowly but completely absorbed, with bioavailability in the range of 100%. It is approximately 50% protein bound with a volume of distribution of 0.5 L/kg. Phenobarbital has a long half-life of 96 hours, with no known active metabolites.

Sedation is common at therapeutic concentrations for the first 2 to 3 weeks of therapy, but this side effect disappears with time.

Toxicity due to phenobarbital overdose is characterized by CNS sedation and reduced respiratory function. Mild symptoms characterized by ataxia, nystagmus, fatigue, or attention loss, occur at blood concentrations >40 mcg/mL.

Symptoms become severe at concentrations > or =60 mcg/mL. Toxicity becomes life-threatening at concentrations >100 mcg/mL. Death usually occurs due to respiratory arrest when pulmonary support is not supplied manually.

There are no known drug interactions that significantly affect the pharmacokinetics of phenobarbital; conversely, phenobarbital affects the pharmacokinetics of other drugs significantly because it induces the synthesis of enzymes associated with the hepatic cytochrome P450 metabolic pathway.

Acute intermittent porphyria attacks may be induced by phenobarbital stimulation of hepatic cytochrome P450.

Reference Values

PHENYTOIN, TOTAL
Therapeutic: 10.0-20.0 mcg/mL
Critical value: > or =30.0 mcg/mL

PHENOBARBITAL
Therapeutic: 10.0-40.0 mcg/mL:
Critical value: > or =60.0 mcg/mL

Interpretation

The therapeutic ranges for adults taking phenytoin have been established at 10 to 20 mcg/mL for total phenytoin (bound plus unbound). The therapeutic range for phenobarbital is10 to 40 mcg/mL. Within these ranges, most people will respond to the drugs without symptoms of toxicity. However, response and side effects will be individual. Dosage determinations and adjustments must be evaluated on a case-by-case basis. A free (unbound) phenytoin level may also need to be ordered when a person has kidney failure, liver disease, hypoalbuminemia, or is taking other medications like aspirin, naproxen, or ibuprofen, in which situation the percentage of free (active) phenytoin may be increased.

Cautions

No significant cautionary statements

Clinical Reference

Phenytoin, Total:
1. Richens A: Clinical pharmacokinetics of phenytoin. Clin Pharmacokinet 1979;4:153-169
2. Moyer TP: Therapeutic drug monitoring. In Tietz Textbook of Clinical Chemistry. Fourth edition. Edited by CA Burtis, ER Ashwood. WB Saunders Company, Philadelphia, 2005, pp 1237-1285

Phenobarbital:
Foero O, Kastrup KW, Nielsen EL, et al: Successful prophylaxis of febrile convulsions with phenobarbital. Epilepsia 1972;13:279-285

Performance

Method Description

Phenytoin, Total:

The assay is based on the kinetic interaction of microparticles in a solution (KIMS). Phenytoin antibody is covalently coupled to microparticles and the drug derivative is linked to a macromolecule. The kinetic interaction of microparticles in solutions is induced by binding of drug-conjugate to the antibody on the microparticles and is inhibited by the presence of phenytoin in the sample. A competitive reaction takes place between the drug conjugate and phenytoin in the serum sample for binding to the phenytoin antibody on the microparticles. The resulting kinetic interaction of microparticles is indirectly proportional to the amount of drug present in the sample.(Package insert: Roche Phenytoin reagent, Roche Diagnostic Corp, Indianapolis, IN)

Phenobarbital:
The assay is based on the kinetic interaction of microparticles in a solution (KIMS). Phenobarbital antibody is covalently coupled to microparticles and the drug derivative is linked to a macromolecule. The kinetic interaction of microparticles in solutions is induced by binding of drug-conjugate to the antibody on the microparticles and is inhibited by the presence of phenobarbital in the sample. A competitive reaction takes place between the drug conjugate and phenobarbital in the serum sample for binding to the phenobarbital antibody on the microparticles. The resulting kinetic interaction of microparticles is indirectly proportional to the amount of drug present in the sample.(Package insert: Roche Phenobarbital reagent, Roche Diagnostic Corp, Indianapolis, IN)

PDF Report
No

Day(s) Performed
Monday through Sunday

Report Available
Same day/1 day

Specimen Retention Time
1 week

Performing Laboratory Location
Rochester

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test has been cleared or approved by the U.S. Food and Drug Administration and is used per manufacturer's instructions. Performance characteristics were verified by Mayo Clinic in a manner consistent with CLIA requirements.

Test Definition: PNYG

Phenytoin, Total and Phenobarbital Group, Serum

CPT Code Information

80184-Phenobarbital
80185-Phenytoin, total

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
PNYG	Phenytoin, Tot and Phenobarbital, S	104596-2

Result ID	Test Result Name	Result LOINC® Value
PBR	Phenobarbital, S	3948-7
PNYA	Phenytoin, Total, S	3968-5