MAYO CLINIC LABORATORIES

Test Definition: FRDIG

Digoxin, Free, Serum

Overview

Useful For

Evaluating recrudescent (breakthrough) digoxin toxicity in renal-failure patients

Assessing the need for more antidigoxin Fab to be administered

Deciding when to reintroduce digoxin therapy

Monitoring patients with possible digoxin-like immunoreactive factors (DLIFs)

Method Name

Ultrafiltration followed by Electrochemiluminescent Immunoassay

NY State Available

Yes

Specimen

Specimen Type

Serum

Specimen Required

Patient Preparation: For 12 hours before specimen collection do not take multivitamins or dietary supplements containing biotin (vitamin B7), which is commonly found in hair, skin, and nail supplements and multivitamins.
Collection Container/Tube:
Preferred: Serum gel
Acceptable: Red top
Submission Container/Tube: Plastic vial
Specimen Volume: 1 mL
Collection Instructions:
1. Draw blood 6 to 8 hours after last dose of digoxin.
2. Serum gel tubes should be centrifuged within 2 hours of collection.
3. 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 1 of the following forms with the specimen:
-Cardiovascular Test Request Form (T724)
-Therapeutics Test Request (T831)

Specimen Minimum Volume

0.6 mL

Reject Due To

Gross hemolysis	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Refrigerated (preferred)	7 days	
	Frozen	180 days	

Clinical & Interpretive

Clinical Information

Digoxin, a widely prescribed cardiac drug, has a narrow therapeutic window (a very small difference exists between therapeutic and toxic tissue concentrations). While excess digoxin can have serious side effects (eg, cardiac dysrhythmias, heart failure, seizures, death), it is one of the few therapeutic drugs for which antidotal therapy is available.(1) In toxic situations, antibody fragment therapy, which involves the administration of antibodies to digoxin (eg, Digibind, Digoxin Immune Fab), is indicated. In manufacturing of Digibind, papain cleaves digoxin-specific IgG antibody into 2 antigen binding-site fragments (Fab fragments). These fragments bind to digoxin, block the active site of the digoxin molecule, and make it unavailable to its receptor molecule and biologically inactive. The Fab fragment-digoxin complex is then excreted by the kidney.

Total digoxin concentration in blood increases approximately 10 to 30 fold after administration of Fab fragments. On the other hand, the unbound (free) fraction, which is responsible for its pharmacological activity, decreases. Traditional digoxin assays performed by immunoassay (eg, DIG / Digoxin, Serum) measure both Fab fragment-bound (inactive) digoxin and free (active) digoxin (ie, total digoxin), and are unsuitable for managing patients when digoxin-specific Fab fragment therapy has been administered. Assays for measurement of free digoxin levels only are necessary in such situations.

The kidneys provide the main route of Fab fragment elimination from the body. In patients with normal renal function, digoxin-specific Fab fragments are excreted in the urine with a biological half-life of 15 to 20 hours. Ordinarily, improvement in signs or symptoms of digoxin intoxication begins within a half hour or less after initiation of Fab fragment therapy. Clearance may be delayed in patients with renal failure. In such patients, toxicity may recur if previously bound drug is released from the Fab fragments, resulting in increased levels of free digoxin.

Digoxin-like immunoreactive factors (DLIFs) are endogenous substances that can cross-react with testing antibodies used in some digoxin immunoassays, causing erroneous results. DLIFs may be seen in certain volume-expanded patients such as neonates, patients with renal or liver disease, and in women in the third trimester of pregnancy being treated with digoxin.(2) DLIFs are strongly bound to proteins and, in this assay, are removed prior to testing.

The following ordering guidelines are offered:

-When creatinine clearance is less than 30 mL/min/surface area: order free digoxin levels daily for 12 days (or until dismissal)
-When creatinine clearance is equal to or above 30 mL/min/surface area (and the patient is not on renal-replacement therapy): order free levels daily for 72 hours, as long as the last level is not supratherapeutic (these patients are expected to have good clearance and a lower risk for reintoxication)
-Also order total digoxin levels every other day during the time periods above, with a goal of determining whether there is correlation between changes in free and total levels.

Reference Values

<16 years:
Therapeutic ranges have not been established for patients who are under 16 years of age. In adults, the suggested serum free digoxin therapeutic range is 0.4-0.9 ng/mL.
Toxic concentration: > or =3.0

> or =16 years:
0.4-0.9 ng/mL
Toxic concentration: > or =3.0 ng/ mL

Interpretation

The target therapeutic level is 0.4 to 0.9 ng/mL. Toxicity may be seen when free digoxin concentrations are 3.0 ng/mL or higher. Pediatric patients may tolerate higher concentrations.

Therapeutic concentrations for free digoxin are 25% lower than therapeutic values for total digoxin due to the separation of protein-bound digoxin in the assay.

Cautions

Patients vary in their responsiveness to digoxin.

Renal dysfunction alters the metabolism of digoxin and antibody-bound digoxin.

It takes 6 to 8 hours after digoxin administration for equilibration between serum and tissue; results obtained from specimens collected less than 6 to 8 hours after the last dose of digoxin should be interpreted with caution.

Digibind (Glaxo Wellcome, Research Triangle Park, NC) is the most common brand of antidigoxin Fab fragments used; other brands are available and may be monitored by this assay.

Clinical Reference

1. Jortani SA, Pinar A, Johnson NA, Valdes R Jr: Validity of unbound digoxin measurements by immunoassays in presence of antidote (Digibind). Clin Chim Acta. 1999;283:159-169
2. DIGIBIND Digoxin Immune FAB (Ovine). Package insert. GlaxoSmithKline; 2003
3. Moyer TP, Boeckx RL, eds: Applied Therapeutic Drug Monitoring. Vol 2. American Association for Clinical Chemistry Press; 1984
4. Jortani SA, Voldes R Jr: Digoxin and its related endogenous factors. Crit Rev Clin Lab Sci. 1997;34:225-274
5. Datta P, Hinz V, Klee G: Comparison four digoxin immunoassays with respect to interference from digoxin-like immunoreactive factors. Clin Biochem. 1996;29(6):541-547
6. Soldin SJ: Free drug measurements. When and why? An overview. Arch Pathol Lab Med. 1999;123:822-823

7. Dickstein K, Cohen-Solal A, Filippatos G, et al: ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Eur Heart J. 2008;29:2388-2442
8. Milone MC, Shaw LM: Therapeutic drugs and their management. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 6th ed. Elsevier; 2018800-831

Performance

Method Description

Free digoxin not bound to the digoxin-specific antibody fragments and not bound to protein is separated from bound digoxin by a 30-kD centrifugal filter device. Free digoxin passes through the filter; bound digoxin is retained in the filter. The filtrate is analyzed for digoxin using a competitive electrochemiluminescence immunoassay that employs a monoclonal antibody directed against digoxin. Digoxin in the specimen competes with the added digoxin derivative labeled with biotin for the binding sites on the ruthenylated antibody-complex. Streptavidin-coated microparticles are added and the mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Application of voltage to the electrode induces the chemiluminescent emission, which is then measured.(Package insert: Elecsys Digoxin, Roche Diagnostics; V3.0, 11/2019)

PDF Report

No

Day(s) Performed

Monday through Sunday

Report Available

Same day/1 day

Specimen Retention Time

7 days

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

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 modified from the manufacturer's instructions. Its performance characteristics were determined by

Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

80163

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
FRDIG	Digoxin, Free, S	3562-6

Result ID	Test Result Name	Result LOINC® Value
FRDIG	Digoxin, Free, S	3562-6