MAYO CLINIC LABORATORIES

Test Definition: SERWB

Serotonin, Blood

Overview

Useful For

In conjunction with, or as an alternative to, first-order tests in the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular flushing (5-hydroxyindoleacetic acid or serum chromogranin A measurements are first-line tests)

Second-order test in the follow-up of patients with known or treated carcinoid tumors using whole blood specimens

Method Name

Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)

NY State Available

Yes

Specimen

Specimen Type

Whole Blood EDTA

Additional Testing Requirements

First-line testing for the diagnosis of carcinoid tumors with symptoms suggestive of carcinoid syndrome consists of urinary serotonin (SERU / Serotonin, 24 Hour, Urine), urinary 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid [5-HIAA], 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum).

Specimen Required

Patient Preparation:

1. Patients should not eat avocados, bananas, butternuts, cantaloupe, dates, eggplant, grapefruit, hickory nuts, honeydew melon, kiwifruit, melon, nuts, pecans, pineapple, plantains, plums, tomatoes, or walnuts, which are high in serotonin for 48 hours before and during collection.
2. Patient should discontinue medications that may elevate urine serotonin concentration including lithium, monoamine oxidase-inhibitors, methyldopa, morphine, and reserpine. Patient should also discontinue use of selective serotonin reuptake inhibitors (SSRI; eg, PROZAC) that can lead to depletion of platelet serotonin levels and result in false-negative urine serotonin tests.

Supplies: Serotonin Tube (T259)
Collection Container/Tube: Lavender top (EDTA)
Submission Container/Tube: Serotonin tube containing ascorbic acid
Specimen Volume: 2.5 mL
Collection Instructions:

1. Immediately after collection, transfer approximately 2.5 mL of whole blood to the serotonin tube and mix well (any volume of whole blood from 1.5-3 mL is acceptable).

2. Immediately freeze specimen (necessary to lyse the red blood cells).

Forms

If not ordering electronically, complete, print, and send an Oncology Test Request (T729) with the specimen.

Specimen Minimum Volume

1.5 mL

Reject Due To

Gross lipemia	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole Blood EDTA	Frozen	90 days	SEROTONIN TUBE

Clinical & Interpretive

Clinical Information

Serotonin (5-hydroxytryptamine) is synthesized from the essential amino acid tryptophan via the intermediate 5-hydroxytryptophan (5-HTP). Serotonin production sites are the central nervous system (CNS), where it acts as a neurotransmitter, and neuroectodermal cells, chiefly gastrointestinal (GI) enterochromaffin cells (EC-cells). The CNS and peripheral serotonin pools are isolated from each other. EC-cell production accounts for 80% of the body's 5-HT content.

Many different stimuli can release serotonin from EC-cells. Once secreted, in concert with other gut hormones, serotonin increases GI blood flow, motility, and fluid secretion. On first pass through the liver, 30% to 80% of serotonin is metabolized, predominately to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted by the kidneys. Ninety percent of the remainder is metabolized to 5-HIAA in the lungs. Of the remaining 10%, almost all is taken up by platelets, where it remains until it is released during clotting, promoting further platelet aggregation.

The main diseases that may be associated with measurable increases in serotonin are neuroectodermal tumors, particularly those arising from EC-cells, which are termed carcinoids. They are subdivided into foregut carcinoids, arising from respiratory tract, stomach, pancreas, or duodenum (approximately 15% of cases); midgut carcinoids, occurring within jejunum, ileum, or appendix (approximately 70% of cases); and hindgut carcinoids, which are found in the colon or rectum (approximately 15% of cases).

Carcinoids display a spectrum of aggressiveness with no clear distinguishing line between benign and malignant. The majority of carcinoid tumors do not cause significant clinical disease. Tumors that behave more aggressively tend to cause nonspecific GI tract disturbances, such as intermittent pain and bloating, for many years before more overt symptoms develop. In advanced tumors, morbidity and mortality relate as much, or more, to the biogenic amines, chiefly serotonin, and peptide hormones secreted, as to local and distant spread. The symptoms of this so-called carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. These

symptoms are at least partly caused by serotonin. Carcinoid syndrome is usually caused by midgut tumors, as foregut and hindgut neoplasms produce far lesser amounts of serotonin. Since midgut tumors drain into the portal circulation, which passes into the liver, symptoms do not usually occur until liver or other distant metastases have developed, bypassing the extensive hepatic first-pass serotonin degradation.

Serotonin production by disseminated carcinoid tumors can sometimes be so substantial that body tryptophan stores become depleted and clinical tryptophan deficiency, resembling pellagra (triad of diarrhea, dementia, and dermatitis), develops.

Diagnosis of carcinoid tumors with symptoms suggestive of carcinoid syndrome rests on measurements of circulating and urinary serotonin, urinary 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid [5-HIAA], 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum), a peptide that is cosecreted alongside specific hormones by neuroectodermal cells.

Reference Values

< or =330 ng/mL

For SI unit Reference Values, see www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html

Interpretation

Metastasizing midgut carcinoid tumors usually produce blood or serum serotonin (5-hydroxytryptamine) concentrations greater than 1000 ng/mL. However, elevations above 400 ng/mL are suggestive of carcinoid tumors as the cause of carcinoid syndrome-like symptoms. Lesser increases may be nonspecific or drug-related (see Cautions).

Only a minority of patients with carcinoid tumors will have elevated serotonin levels. It is usually impossible to diagnose small carcinoid tumors (>95% of cases) without any symptoms suggestive of carcinoid syndrome by measurement of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), or chromogranin A.

In patients with more advanced tumors, circulating serotonin is elevated in nearly all patients with midgut tumors, but only in approximately 50% of those with foregut carcinoids, and in no more than 20% of individuals with hindgut tumors. Foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HTP) decarboxylase activity and, therefore, may produce little if any serotonin. Urinary 5-HIAA is elevated in almost all carcinoid-syndrome patients with midgut tumors, in about 30% of individuals with foregut carcinoids, but almost never in hindgut tumors. Serum chromogranin A measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though serotonin and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with foregut and midgut tumors. Therefore, to achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, serotonin in serum/blood, 5-HIAA in urine, and serum chromogranin A should all be measured. In most cases, if none of these 3 analytes is elevated, carcinoids can be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests, such as urinary serotonin measurement, will be required. An example would be a non-chromogranin-secreting foregut tumor that only produces 5-HTP, rather than serotonin. In this case, circulating chromogranin, serotonin levels, and urinary 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to serotonin, leading to high urinary serotonin levels.

Disease progression can be monitored in patients with serotonin-producing carcinoid tumors by measurement of serotonin in blood. However, at levels above approximately 5000 ng/mL, the serotonin storage capacity of platelets becomes limiting, and there is no longer a linear relationship between tumor burden and blood serotonin levels. Urinary

5-HIAA and serum chromogranin A continue to increase in proportion to the tumor burden to much higher serotonin production levels and are, therefore, better suited for follow-up in patients with extensive disease.

Cautions

Since most circulating serotonin (5-hydroxytryptamine) is contained in platelets, the preferred specimens for measurement either include all or most of the platelets (ie, whole blood and platelet-rich plasma) or consist of serum from completely clotted specimens, a process that releases nearly all serotonin from platelets. "Ordinary" or platelet-poor plasma specimens are not suitable.

Medications that may elevate serotonin concentrations include lithium, monoamine oxidase inhibitors, methyldopa, morphine, and reserpine. The observed levels are usually less than400 ng/mL. Selective serotonin reuptake inhibitors (SSRI; eg, fluoxetine) can lead to depletion of platelet serotonin levels and result in false-negative serum and blood serotonin tests. The effects of drugs are more marked on urinary serotonin and 5-hydroxyindoleacetic acid (5-HIAA) levels than on serum and blood serotonin levels.

Serotonin- or tryptophan-rich foods (eg, avocados, bananas, plums, walnuts, pineapple, eggplant, plantain, tomatoes, hickory nuts, kiwi, dates, grapefruit, cantaloupe, and honeydew melon) do not contribute significantly to serum or blood serotonin measurements, but can elevate platelet-poor plasma serotonin, urinary serotonin, and urinary 5-HIAA levels markedly (up to 10-fold).

Clinical Reference

1. Kema IP, Schellings AM, Meibotg G, Hoppenbrouwers CJ, Muskiet FA: Influence of a serotonin- and dopamine-rich diet on platelet serotonin content and urinary excretion of biogenic amines and their metabolites. Clin Chem. 1992 Sep;38(9):1730-1736
2. Kema IP, de Vries EG, Muskiet FA: Clinical chemistry of serotonin and metabolites. J Chromatogr B Biomed Appl. 2000 Sep;747:33-48
3. Meijer W, Kema I, Volmer M, Willemse PH, de Vries EG: Discriminating capacity of indole markers in the diagnosis of carcinoid tumors. Clin Chem. 2000 Oct;46(10):1588-1596
4. Ganim RB, Norton JA: Recent advances in carcinoid pathogenesis, diagnosis and management. Surg Oncol. 2000 Dec;9(4):173-179
5 Eisenhofer G, Grebe S, Cheung NKV. Monamine-producing tumors. In: Rifai N, Horvath AR, Wittwer C, eds Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2017:chap 63
6. Brand T, Anderson GM: The measurement of platelet-poor plasma serotonin: A systematic review of prior reports and recommendations for improved analysis. Clinical Chemistry. 2011 Oct; 57(10):1376-1386
7. Liu EH, Solorzano CC, Katznelson L, Vinik AI, Wong R, Randolph G: AACE/ACE disease state clinical review: diagnosis and management of midgut carcinoids. Endocr Pract. 2015 May; 21(5):534-545

Performance

Method Description

Serotonin is extracted from the sample using reversed-phase solid-phase extraction (SPE). Separation is completed using a Bond Elut C18 SPE cartridge and is eluted with 40% acetonitrile:1 mM ammonium acetate:0.1% formic acid. The eluate is analyzed using liquid chromatography tandem mass spectrometry and quantified using a stable isotope-labeled internal standard, d4-serotonin.(Carling RS, Degg TS, Allen KR, et al: Evaluation of whole blood serotonin and plasma and

urine 5-hydroxyindole acetic acid in diagnosis of carcinoid disease. Ann Clin Biochem 2002;39:577-582; Johnsen E, Leknes S, Wilson SR, Lundanes E. Liquid chromatography-mass spectrometry platform for both small neurotransmitters and neuropeptides in blood, with automatic and robust solid phase extraction. Sci Rep. 2015 Mar 20;5:9308. doi: 10.1038/srep09308)

PDF Report
No

Day(s) Performed
Monday, Wednesday, Friday

Report Available
5 to 8 days

Specimen Retention Time
3 months

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 was developed, and its performance characteristics 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
84260

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
SERWB	Serotonin, B	2939-7

Result ID	Test Result Name	Result LOINC® Value
84373	Serotonin, B	2939-7