MAYO CLINIC LABORATORIES

Test Definition: SER

Serotonin, Serum

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

Method Name

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

NY State Available

Yes

Specimen

Specimen Type

Serum

Additional Testing Requirements

First-line testing for the diagnosis of carcinoid tumors with symptoms suggestive of carcinoid syndrome consists of urinary 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid, 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum). Serotonin in whole blood (SERWB / Serotonin, Blood), serum (SER / Serotonin, Serum), and urine (SERU / Serotonin, 24 Hour, Urine) are useful in conjunction with these first-line tests.

Specimen Required

Patient Preparation: Patient **should not** take medications that may elevate serotonin levels, including lithium, monoamine oxidase inhibitors, methyldopa, morphine, and reserpine, or selective serotonin reuptake inhibitors (SSRI, eg, PROZAC) which can lead to depletion of platelet serotonin levels and result in false-negative serotonin results for a minimum of 72 hours before specimen collection. Some drugs with longer half-lives (i.e. fluoxetine) can require months after discontinuation for serotonin levels to return to baseline.
Supplies: Sarstedt Aliquot Tube, 5 mL (T914)
Collection Container/Tube:
Preferred: Red top
Acceptable: Serum gel
Submission Container/Tube: Plastic vial
Specimen Volume: 2.5 mL
Collection Instructions: Centrifuge as soon as blood has clotted and aliquot serum into a plastic vial.

Specimen Minimum Volume

1.1 mL

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Refrigerated (preferred)	21 days	
	Ambient	4 days	
	Frozen	90 days	

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 (EC) cells. The CNS and peripheral serotonin pools are isolated from each other. EC-cell production accounts for 80% of the body's serotonin 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). The enzyme 5-HTP decarboxylase, which converts the intermediate 5-HTP to serotonin, is present in midgut tumors but is absent or present in low concentrations in foregut and hindgut tumors.

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. The 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 less 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 whole blood, serum, and urinary serotonin, urinary 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid, 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 =230 ng/mL

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 than 400 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 blood and serum 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).(1)

Clinical Reference

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9. Stiefel R, Lehmann K, Winder T, Siebenhüner AR. What have we learnt from the past - would treatment decisions for GEP-NET patients differ between 2012 to 2016 by the new recommendations in 2022?. BMC Cancer. 2023;23(1):148. Published 2023 Feb 13. doi:10.1186/s12885-023-10567-1

Performance

Method Description

Isotopically labeled internal standard (serotonin-D4) is added to the sample. Serotonin and the internal standard are

enriched using solid phase extraction and analyzed using liquid chromatography-tandem mass spectrometry.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Monday, Wednesday, Friday

Report Available
5 to 8 days

Specimen Retention Time
2 weeks

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Superior Drive

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. It 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
SER	Serotonin, S	27057-9

Result ID	Test Result Name	Result LOINC® Value
84395	Serotonin, S	27057-9