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 serum specimens.

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 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 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.

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 into plastic vial.

Reject Due To

- Gross hemolysis: OK
- Gross lipemia: OK
- Gross icterus: OK

Specimen Minimum Volume

1.1 mL

Specimen Stability Information

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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 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, predominantly 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, in particular, 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. Those 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 circulating and urinary serotonin, urinary 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid [5-HIAA], 24 Hour, Urine), and serum chromogranin A (CGA / 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 5-HT measurements but can elevate platelet-poor plasma serotonin, urinary serotonin, and urinary 5-HIAA levels markedly (up to 10-fold).
Test Definition: SER
Serotonin, S

Clinical Reference


Performance

Method Description

PDF Report
No

Specimen Retention Time
3 months
Test Definition: SER
Serotonin, S

Performing Laboratory Location
Rochester

Fees & Codes

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

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