

COMMUNIQUE

IMPROVING PATIENT CARE THROUGH ESOTERIC LABORATORY TESTING

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Update on Serotonin

Serotonin pathways regulate many systems in the body, and disturbances in the serotonergic (activated by or capable of liberating serotonin) system result in a wide range of problems. Drugs that affect the serotonergic system are commonly used to treat psychiatric disorders, and inherited differences in serotonin metabolism may alter patients' responses to these drugs. In this review, we discuss serotonin metabolism, serotonin syndrome, and new serotonin-related genetic tests (pharmacogenetics).

Serotonin Metabolism

Serotonin (5-hydroxytryptamine; 5-HT) is synthesized from the amino acid tryptophan. The body has 3 main serotonin pools: the central nervous system (CNS), gastrointestinal (GI) enterochromaffin cells, and platelets.

Serotonin and the Central Nervous System

Serotonin, a neurotransmitter, is an important regulator of the autonomic nervous system (including temperature regulation and GI motility),

neuromuscular activity, cognitive function, and mood control. Serotonin is released from presynaptic neurons and binds to postsynaptic serotonin receptors, thereby exciting the postsynaptic neurons. The serotonin transporter then carries serotonin back into the presynaptic neuron for subsequent reuse. Conversely, the enzyme monoamine oxidase (MAO) reduces presynaptic serotonin levels by deamination (Figure 1).

Serotonin in Enterochromaffin Cells

Serotonin released from enterochromaffin cells exerts a strong influence on the GI tract by increasing GI blood flow, motility, and fluid secretion. On its 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. Most of the remaining serotonin (90%) is metabolized in the lungs, also to 5-HIAA. Approximately 10% is taken up by platelets, where it remains until it is released during the coagulation process.

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- #88672 *API2/MALT1, mRNA Detection by Reverse Transcription-PCR*
- #80678 *Chorionic Gonadotropin for Pregnancy, Serum*

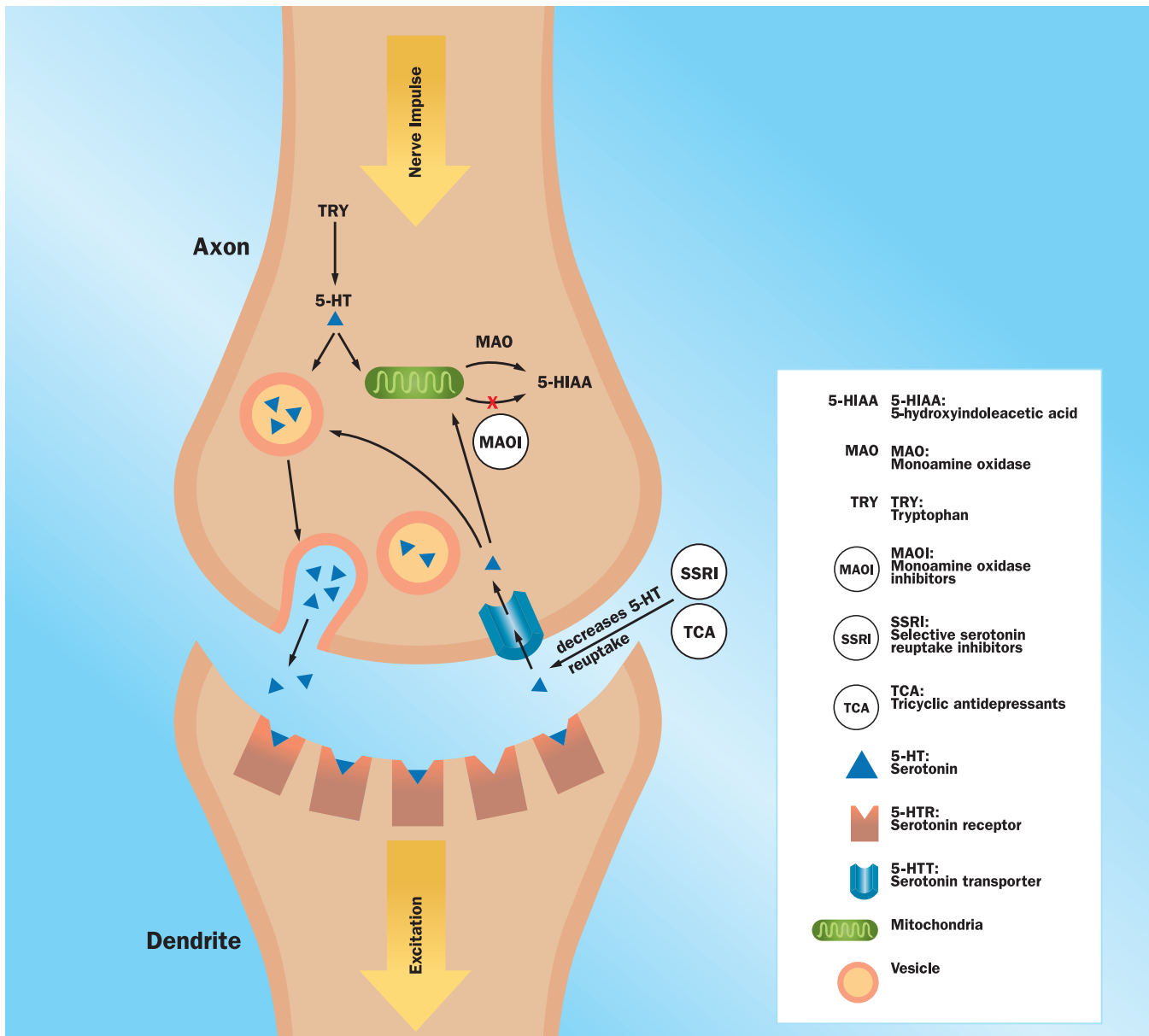


Figure 1. Diagram of neurosynaptic serotonin (5-HT).

Serotonin in Platelets

Serotonin is stored in the platelets' dense granules and released during platelet activation. It stimulates platelet aggregation and causes other local and systemic effects including vasodilation and constriction, blood pressure changes, and bronchoconstriction.

Serotonin and Psychiatric Disorders

Anxiety and depression are often treated with drugs that increase CNS serotonin levels, either by:

- Reducing serotonin deamination (eg, monoamine oxidase inhibitors [MAOI])
- Increasing serotonin precursors (eg, lithium)
- Acting as serotonin agonists (eg, trazodone)

- Increasing serotonin levels in the nerve synapses (eg, tricyclic antidepressants [TCAs], such as amitriptyline [Elavil], imipramine [Tofranil], and desipramine [Norpramin], and the selective serotonin reuptake inhibitors [SSRIs], such as citalopram [Celexa], fluoxetine [Prozac], paroxetine [Paxil], sertraline [Zoloft], and escitalopram [Lexapro]).

Use of these drugs has become increasingly widespread. However, some patients are nonresponsive or respond slowly to these medications, while other patients may develop serious side effects (eg, serotonin syndrome, cardiac dysrhythmias, hypotension, convulsions, CNS depression, or worsening of depression). Antidepressant drug selection may be more effectively guided by pharmacogenetic testing. Molecular tests are currently available for genes encoding the hepatic enzymes responsible for drug metabolism (cytochrome P450 enzymes), for the serotonin receptor, and for the serotonin transporter.¹

Cytochrome P450-mediated Metabolism of Serotonergic Drugs

Metabolism of many drugs is accomplished by cytochrome P450 (CYP) enzymes, a group of enzymes located predominantly in the liver (Table 1). Of the CYP enzymes, CYP2D6 is primarily responsible for the metabolism of a large number of commonly prescribed drugs, including the SSRIs and TCAs.

CYP2D6-mediated drug metabolism is highly variable, and inherited differences have been described. Individuals without inactivating polymorphisms, deletions, or duplications are considered normal (referred to as extensive metabolizers), designated as *CYP2D6**1/*1. Some individuals have altered *CYP2D6* gene sequences (polymorphisms) that result in synthesis of enzyme with decreased or absent catalytic activity. These individuals metabolize SSRIs and TCAs poorly and may experience significant medication side effects due to prolonged exposure to the active form of the

drug. Other individuals demonstrate accelerated metabolism and may not experience the desired therapeutic effects because the drug is rapidly inactivated and/or eliminated. Individuals with extra copies (duplication) of the functional *CYP2D6* gene demonstrate accelerated metabolism (ultrarapid metabolizers).

A number of polymorphisms have been identified in the *CYP2D6* gene that result in enzymatic deficiencies (Table 2). The frequency of these polymorphisms varies within major ethnic groups. *CYP2D6* polymorphisms that result in poor metabolism are found in 7% to 10% of Caucasians, 2% of Africans and African Americans, and 1% of Asians. Individuals who are homozygous (2 copies of 1 abnormality) or compound heterozygous (1 copy of 2 different abnormalities) for the polymorphisms associated with reduced enzyme activity are poor metabolizers. Individuals who are heterozygous, with 1 normal gene and 1 polymorphic gene, will have a metabolism that is intermediate, between the extensive and poor metabolizers.

Identification of a patient's *CYP2D6* genotype may allow appropriate dosing adjustments ([#83180 Cytochrome P450 2D6 Genotyping](#)). Patients who are poor metabolizers may need lower than usual doses to achieve optimal response while avoiding toxicity. Patients who are ultrarapid metabolizers may benefit from increased doses or conversion to other drugs that are not primarily metabolized by CYP2D6. A complicating factor in correlating CYP2D6 genotype with phenotype is that many drugs (or their metabolites) may reduce CYP2D6 catalytic activity (Table 1). For example, an individual with an inherited pattern consistent with intermediate metabolizer status for the antidepressant amitriptyline (metabolized by CYP2D6) may act as a poor metabolizer if he or she also is taking a drug that decreases CYP2D6 activity such as celecoxib or quinidine. Consequently, it is important to interpret the results of CYP testing in the context of other coadministered drugs, as individuals may require dosing changes greater or less than predicted based upon genotype alone.

Drugs That Undergo Metabolism By CYP2D6:

Alpha-blocker: alprenolol, timolol

Analgesic: codeine, oxycodone, tramadol

Anticonvulsant: felbamate, mephobarbital

Antidepressant: amitriptyline, clomipramine, desipramine, duloxetine, fluoxetine, fluvoxamine, imipramine, mirtazapine, nortriptyline, paroxetine, sertraline, venlafaxine

Antidiabetic: phenformin

Antiestrogen: tamoxifen

Antihypertensive: diltiazem

Antipsychotic: aripiprazole, chlorpromazine, haloperidol, perphenazine, risperidone, thioridazine

Antitussive: dextromethorphan

Beta-blocker: labetalol, metoprolol, propranolol

Cardioactive: disopyramide, encainide, flecainide, lidocaine, mexiletine, propafenone

Norepinephrine reuptake inhibitors: atomoxetine

Stimulant: amphetamine

Coadministration may decrease the rate of elimination of other drugs metabolized by CYP2D6

Drugs Known To Increase CYP2D6 Activity:

Dexamethasone

Coadministration of this drug increases the rate of excretion of CYP2D6-metabolized drugs, reducing the other drugs' effectiveness.

Drugs Known To Decrease CYP2D6 Activity:

Analgesic: celecoxib, methadone

Antidepressant: bupropion, clomipramine, citalopram, duloxetine, fluoxetine, paroxetine, and sertraline

Antiemetic: metoclopramide

Antineoplastic: doxorubicin

Antipsychotic: chlorpromazine, haloperidol

Antiretroviral: indinavir, ritonavir

Antistroke: ticlopidine

Cardioactive: amiodarone, quinidine

H-1 blocker: cimetidine, ranitidine

Stimulant: cocaine

Sympathomimetic: chlorpheniramine

Coadministration will decrease the rate of metabolism of CYP2D6-metabolized drugs, increasing the possibility of toxicity.

Table 1. Some of the known CYP2D6 metabolism and drug relationships.

Serotonin Receptor Genotype

The effects of serotonin occur after it binds to serotonin receptors, a large and diverse family of G protein-coupled receptors.² At least 7 groups of serotonin receptors, each with multiple polymorphisms, have been described.² Receptor proteins encoded by these gene variants may demonstrate differing serotonin binding affinity, differing signal transduction capabilities, or differing numbers of receptors.³ Such differences may play a role in individuals' predispositions to some psychiatric disorders as well as differences in drug response.

Mayo has developed a test for serotonin receptor gene variants, [#83303 Serotonin Receptor Genotype \(HTR2A and HTR2C\)](#). The test identifies 2 *HTR2A* variants and 1 *HTR2C* variant (Table 3). Patients who carry these variants have been shown to manifest adverse responses to some psychiatric drugs. For example, variation in the *HTR2A* gene has been reported to affect

response to SSRIs, putting the patient at increased risk for adverse drug reactions.³ Variations in the *HTR2A* and *HTR2C* genes have been associated with increased risk of tardive dyskinesia, a common and troubling medication side effect, in schizophrenic patients.^{4,5} Conversely, the presence of the *HTR2A* allele and *HTR2C* allele have been reported to predict favorable response to therapy with clozapine, an antipsychotic agent.⁶ A variant in the promoter of *HTR2C* (-759C) is associated with significant weight gain when treated with many antipsychotic medications.¹³

This gene test may be useful in guiding antidepressant and antipsychotic medication choices in some patients. It also may be used as a follow-up test to further evaluate patients whose phenotype (drug response) is discordant with their CYP450 genotype. Further studies are needed to determine the appropriate use of such tests and to determine if assays for additional serotonin receptor gene variants are needed.

CYP2D6 Allele	Nucleotide Change	Effect on Enzyme Metabolism
*1	None (wild type)	Extensive metabolism (normal)
*2	2850C→T	Decreased activity
*2A	2850C→T and -1584C→G	Slightly increased activity
*3	2549A→del	No activity
*4	1846G→A	No activity
*5	Gene deletion	No activity
*6	1707T→del	No activity
*7	2935A→C	No activity
*8	1758G→T	No activity
*9	2613delAGA	Decreased activity
*10	100C→T	Decreased activity
*11	883G→C	No activity
*12	124G→A	No activity
*17	1023C→T	Decreased activity
Gene duplication		Depends on the allele

Table 2. CYP2D6 Variants

Gene	Nucleotide Change	Amino Acid Change
HTR2A	74C→A	Thr25Asp
	1354C→T	His452Tyr
HTR2C	796C→G	Cys23Ser
	-759C→T	Promoter polymorphism

Table 3. #83303 *Serotonin Receptor Genotype (HTR2A and HTR2C) assay.*

Serotonin Transporter Genotype Assay

The serotonin transporter modulates neurotransmission by facilitating removal of serotonin from the synapse of serotonergic neurons, resulting in serotonin reuptake into the presynaptic neuron. SSRIs, which are commonly prescribed to treat depression and other psychiatric disorders, act by blocking the action of the serotonin transporter, thereby decreasing serotonin reuptake and increasing the levels of serotonin at the nerve synapse.

A 42- to 45-base pair promoter insertion/deletion polymorphism in the *SLC6A4* gene, which encodes the serotonin transporter, produces alleles described as long or short. The long allele results in a 60% increased production of the transporter molecule. Individuals homozygous for the short allele may respond more slowly to SSRIs than individuals who carry the long allele. For example, individuals with the short allele (l/s or s/s) may require up to 12 weeks to demonstrate a SSRI response, whereas individuals homozygous for the long allele (l/l) may respond in 3 to 4 weeks.⁸ Due to their low transporter levels, s/s individuals recover less serotonin from the synapse following neuronal activation than l/l individuals. Consequently, over time, less serotonin is available for release into the synapse, resulting in poorer activation of the postsynaptic neuron. Additionally, s/s individuals may experience more adverse effects than l/s or l/l individuals.⁸

#83302 *Serotonin Transporter Genotype, Blood* may prove useful in evaluating patients who have treatment-resistant depression, predicting response time to improvement with SSRIs, and identifying patients who might respond better to non-SSRI antidepressants.

Serotonin Syndrome

Serotonin syndrome is a potentially life-threatening complication of some medications, including the SSRIs. The syndrome is characterized by sudden onset of mental status and behavioral changes, autonomic dysfunctions, and neuromuscular problems, typically within 24 hours of initiating treatment or changing dosage. Table 4 provides a listing of many of the typical symptoms of serotonin syndrome.

Serotonin syndrome is caused by medication-induced (iatrogenic) overstimulation of serotonin receptors with subsequent systemic activation of the serotonergic system. A wide variety of medications can initiate these reactions by acting as serotonin precursors or agonists (eg, L-dopa, lithium, trazodone), by stimulating serotonin release (eg, amphetamines, cocaine, "ecstasy"), by inhibiting serotonin reuptake (eg, SSRIs, TCAs, dextromethorphan), or by decreasing serotonin metabolism (eg, MAOIs). Alternatively, a combination of these mechanisms also may cause serotonin syndrome. For example, the commonly

used over-the-counter supplement St. John's Wort, when taken with SSRIs, may result in serotonin syndrome. Dextromethorphan can also cause serotonin syndrome in patients taking SSRI's. CYP polymorphisms may also play a role in serotonin syndrome. Drug levels of the offending agent may be higher in patients who are CYP2D6 poor metabolizers. While most patients with serotonin syndrome have been taking 2 or more medications, it can occur with a single agent. (Table 5)

The differential diagnosis of the triad of the mental, autonomic, and neuromuscular changes seen in serotonin syndrome is very long and includes most causes of delirium, including poisoning, drugs of abuse overdose, infections, central nervous system disease, liver and renal failure, psychiatric disorders, heatstroke, trauma, and neuroleptic malignant syndrome.* The diagnosis is one of exclusion and requires a high index of suspicion. Because most cases are mild, the disorder may be underdiagnosed.

No laboratory tests are specific for serotonin syndrome. Nonspecific laboratory abnormalities include elevated skeletal muscle enzymes, abnormal liver function tests, and elevated white blood cell counts. Many other laboratory abnormalities may be seen, associated with the secondary complications of disseminated intravascular coagulation, renal failure, and acidosis. In patients with reduced CYP metabolism, specific drug levels may be increased.¹³ While excessive serotonin is responsible for the syndrome, blood or urine serotonin assays are not helpful because symptoms are caused by excess serotonin concentrations at the nerve synapses; blood and urine serotonin levels are not increased.

Mental Symptoms	
Agitation	
Anxiety	
Coma	
Confusion	
Dizziness	
Hallucinations	
Insomnia	
Lethargy	
Seizures	
Autonomic Symptoms	
Diarrhea	
Dilated/unreactive pupils	
Hypertension	
Hyperthermia	
Nausea	
Sweating	
Tachycardia	
Vomiting	
Neuromuscular Symptoms	
Ataxia	
Hyperreflexia	
Myoclonus	
Restlessness	
Rigidity	
Tremor	

Table 4. Signs and symptoms associated with serotonin syndrome.

* Neuroleptic malignant syndrome (NMS), another potentially life-threatening disorder, may be clinically confused with serotonin syndrome. NMS occurs as a reaction to the antipsychotic medications, referred to as neuroleptics or neuroleptic agents (eg, haloperidol, chlorpromazine, clozapine, risperidone). These agents act via the dopaminergic neurotransmission system. NMS occurs in approximately 1% of patients taking these agents, typically within 3 to 9 days of therapy.¹⁴ While NMS is currently thought to be caused by an idiosyncratic drug reaction, genetic susceptibility is possible.¹⁵ Currently, no specific laboratory tests are available. Diagnosis relies on clinical history and ruling out other causes.

Drugs Associated With Serotonin Syndrome

Amantadine (Symmetrel)	MDMA (ecstasy)
Amphetamines	Meperidine (Demerol)
Brofaromine (Consonar)	Meta-chlorophenylpiperazine (mCPP)
Bromocriptine (Parlodel)	Mirtazapine (Remeron)
Bupropion (Wellbutrin)	Moclobemide (Manerix)
Buspiron (Buspar)	Monoamine oxidase inhibitors (eg, isocarboxazid)
Citalopram (Celexa)	Nortriptyline (Pamelor)
Clomipramine (Anafranil)	Olanzapine (Zyprexa)*
Cocaine	Pargyline (Eutonyl)
Dextromethorphan*	Paroxetine (Paxil)
Fenfluramine	Phenelzine (Nardil)
Fluoxetine (Prozac)	Resperidone (Risperdal)
Fluvoxamine (Luvox)	Selegiline (Eldepryl)
Imipramine (Tofranil)	Sertraline (Zoloft)
Isocaboxazid (Marplan)	Sumatriptan (Imitrex)
Levodopa (L-dopa)	Tranlycypromine (Parnate)*
Lithium	Trazodone (Desyrel)
LSD (lysergic acid diethylamide)	Tricyclic antidepressants (eg, Amitriptyline [Elavil])
L-tryptophan	Venlafaxine (Effexor)

Table 5. Some of the drugs or drug groups that may cause or contribute to the development of serotonin syndrome.^{9,12}

* These drugs, when used in combination with other drugs from this list, appear to cause serotonin syndrome more frequently than other drugs on the list.

Treatment consists of supportive care (eg, intravenous therapy, careful monitoring) and removal of the offending agent(s). Once the inciting agent(s) has been removed, recovery is usually rapid. Other agents may be used to shorten the duration of symptoms, although most patients recover in 24 hours with supportive care alone.

Prevention is the goal for this potentially serious disorder. This requires knowledge of possible drug interactions for all prescribed medications, avoidance of concomitant use of more than 1 drug known to affect the serotonergic system, allowing the patient's system to clear 1 such drug before starting another, and cautioning patients to disclose all medications and therapeutic and nutritional supplements to their physicians. As well, patients must be advised of the risks of self-medication and counseled to avoid adding new medications without physician review. CYP testing may be useful to select appropriate therapeutic agents for some patients.

For additional information about the potential for adverse drug reactions, consult MedWatch, the Federal Drug Administration (FDA) Safety Information and Adverse Event Reporting Program that serves both health care professionals and the public (www.fda.gov/medwatch).

Conclusion

With the growing use of psychiatric drugs and increased awareness of the genetic variations in CYP drug metabolism, there must evolve an equal awareness of the impact of these 2 factors on serotonin levels and the risks for developing serotonin syndrome. Laboratory tests, including genotyping, can provide critical information for appropriately matching patients with therapeutic drugs. Mayo Medical Laboratories (MML) and Mayo Clinic are actively involved in clinical research and test development to evaluate the most appropriate use of existing tests and to develop new tests to guide patient management. See Table 6 for a list of CYP and serotonin genotyping tests available from MML to assist you in evaluating your patients. For additional information about serotonin and CYP testing, please contact Mayo Lab Inquiry at 800-533-1710.

Cytochrome P450	
#83180	Cytochrome P450 2D6 Genotyping
#83639	Cytochrome P450 2C19 Genotyping
#83652	Cytochrome P450 2C9 Genotyping
Serotonin Genotyping	
#83303	Serotonin Receptor Genotype (HTR2A and HTR2C)
#83302	Serotonin Transporter Genotype, Blood

Table 6. MML tests for cytochrome P450 and serotonin genotyping.

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ASK US

Question: *Is serotonin syndrome the same as carcinoid syndrome?*

Answer: No, these are 2 different disorders. Serotonin syndrome, as discussed in this month's feature article, is a drug-related disorder of serotonin metabolism, whereas carcinoid syndrome is a disease of excess serotonin production by tumor cells.

Carcinoids are neoplasms derived from serotonin-secreting neuroectodermal cells. Most carcinoid tumors do not cause significant clinical disease. Those tumors that behave more aggressively tend to cause nonspecific gastrointestinal disturbances, such as intermittent pain and bloating, for many years before more overt symptoms develop. In advanced cases, morbidity and mortality relate as much, or more, to circulating serotonin levels than to tissue and organ damage caused by tumor growth. The symptoms of carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. These symptoms are at least partly caused by excess serotonin.

Question: *What laboratory tests are used to diagnose carcinoid syndrome?*

Answer: The laboratory diagnosis of carcinoid syndrome relies on measurements of circulating and urinary serotonin, urinary 5-hydroxyindoleacetic acid (5-HIAA) (serotonin's main metabolite), and serum chromogranin A (a peptide that is secreted by neuroectodermal cells). Metastatic carcinoid tumors often show very high levels of serum serotonin (>1000 ng/mL). In the presence of appropriate symptoms, serum serotonin values >400 ng/mL are suggestive of the presence of a carcinoid tumor. However, normal levels are seen in most patients.

Question: *Do medications associated with serotonin syndrome cause elevations in serum serotonin?*

Answer: As discussed in this month's feature, serum serotonin is not used to evaluate patients with possible serotonin syndrome. This is because the disease-causing serotonin elevations in serotonin syndrome occur at the neurosynaptic junction and circulating serotonin levels are usually not increased. While some medications (eg, MAOIs, methyl dopa, morphine, lithium, reserpine) may elevate serotonin concentrations, the resulting serum serotonin levels are usually modest (<400 ng/mL; normal reference value for serum serotonin <230 ng/mL). Conversely, some drugs (eg, SSRIs) may cause a decrease in serotonin levels.

Question: *Are there dietary restrictions for serotonin testing?*

Answer: Serotonin- or tryptophan-rich foods (avocados, bananas, plums, walnuts, pineapple, eggplant, plantain, tomatoes, hickory nuts, kiwi, dates, grapefruit, cantaloupe, and honeydew melon) do not contribute significantly to blood serotonin measurements, but can elevate results obtained in urine and plasma-based serotonin assays, as well as urinary 5-HIAA levels. Medications that alter serotonin levels should also be avoided prior to specimen collection, if possible.

2006 EDUCATION CALENDAR

Upcoming Education Conferences . . .

Bleeding and Thrombosing Diseases - Wet Workshop
August 2, 2006
The Kahler Grand Hotel • Rochester, MN

Bleeding and Thrombosing Diseases Conference
August 3–4, 2006
The Kahler Grand Hotel • Rochester, MN

Practical Surgical Pathology
September 14–16, 2006
Siebens Building • Mayo Clinic, Rochester, MN

State-of-the-Art Thrombophilia
September 21–23, 2006
Siebens Building • Mayo Clinic, Rochester, MN

Quality Phlebotomy: Back to the Basics
October 2, 2006
Hilton Dallas/Park Cities • Dallas, TX

Practical Spirometry
October 12–13, 2006
Radisson Hotel & Suites • Chicago, IL

Real-Time PCR for the Clinical Microbiology Laboratory
October 26–27, 2006
Siebens Building • Mayo Clinic, Rochester, MN

Practical Spirometry
November 14–15, 2006
Siebens Building • Mayo Clinic, Rochester, MN

Biomarkers of Cardiovascular Risk: State of the Art
November 16–17, 2006
Siebens Building • Mayo Clinic, Rochester, MN

Interactive Satellite Programs . . .

Genomics and Proteomics: An Update
September 12, 2006
Presenter: *David B. Schowalter, MD, PhD*

An Approach to Evaluation of Bleeding Disorders
October 3, 2006
Presenter: *Rajiv K. Pruthi, MBBS*

Update on Contemporary Pain Management of the Patient with Cancer
November 14, 2006
Presenters: *Marc A. Huntoon, MD*
Toby N. Weingarten, MD

Update on Cardiovascular Markers
December 12, 2006
Presenter: *Allan S. Jaffe, MD*

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