MEDICINE CABINET

How medications affect thyroid function

Betty J Dong
University of California, San Francisco
School of Pharmacy
505 Parnassus Ave
San Francisco, CA
94143-0622

Correspondence to:
Dr Dong
bjdong@itsa.ucsf.edu

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Abnormal results of thyroid function tests are common in clinical practice. The diagnosis of thyroid dysfunction is easily made, especially if the clinical signs and symptoms of thyroid dysfunction are also present. In elderly patients aged 65 years and older, who often have atypical presentations, the diagnosis of thyroid dysfunction is more difficult. Sometimes laboratory findings are abnormal because of a patient's use of medications or the presence of unrelated and nonthyroidal medical illnesses. Many abnormalities identified by thyroid laboratory tests can be caused by various illnesses that do not directly involve the thyroid gland. This "euthyroid sick syndrome" occurs in as many as 70% of patients who have been admitted to a hospital.[1,2] Recognition is critical because therapy is not necessary and may be detrimental. There results of thyroid function tests often revert to normal once the patient recovers from the illness.

In this review, I focus on medications that interfere with the proper interpretation of thyroid function test results, cause thyroid illnesses, influence levothyroxine requirements, and impair absorption of exogenous levothyroxine.

THYROID FUNCTION TESTS

Common laboratory tests used in the assessment and diagnosis of thyroid disorders include measuring the circulating thyroid hormone concentrations, evaluating the integrity of the pituitary negative-feedback system, measuring thyroid antibody concentrations, and evaluating radioactive iodine uptake and scans. Tests to measure circulating thyroid hormone concentrations can include total thyroxine (T_4), total triiodothyronine (T_3), free thyroxine index, free T_4 (FT_4), and free T_3 (FT_3).

Total T_4 and total T_3 measurements are less accurate because several medications can interfere (for example, estrogen and estrogen-containing birth control pills, tamoxifen citrate, heroin, methadone hydrochloride, fluouracil, mitotane, androgens, anabolic steroids, nicotinic acid, and glucocorticoids) scan medical conditions (such as the nephrotic syndrome) that alter thyroid-binding globulin and confuse results. Measurement of the total T_3 level is still frequently used because many laboratories cannot perform FT_3 measurements.

The measurement of the free T_4 index and FT_4level should replace measurements of the total T_4 level. The free hormone concentrations also accurately represent the thyroid state.

The integrity of the pituitary negative-feedback system is evaluated by measuring levels of thyrotropin (the thyroid-stimulating hormone). This is the most sensitive test for screening, diagnosis, and monitoring of thyroid dysfunction because thyrotropin levels may become abnormal before corresponding changes occur in the circulating free thyroid hormone levels. The diagnosis of primary hypothyroidism is confirmed by raised concentrations of thyrotropin and subnormal FT_4 concentrations. Similarly, findings of an undetectable concentration of thyrotropin and raised FT_4 concentration are diagnostic of hyperthyroidism. In subclinical thyroid disease, however, the FT_4 concentration remains normal whereas in subclinical hypothyroidism, the thyrotropin concentration is raised and, in subclinical hyperthyroidism, it is suppressed below normal.

The measurement of the total or FT_3 level is useful to document possible hyperthyroidism, especially if FT_4 levels are normal and the thyrotropin level is suppressed. Furthermore, the T_3 level should not be monitored in hypothyroidism because many medications and illnesses that do not involve the thyroid can block peripheral conversion of T_4 to T_3 and produce a low concentration of T_3. In addition, T_3 concentrations can be normal in hypothyroidism.

MEDICATIONS THAT INTERFERE WITH THYROID FUNCTION TESTING

Dopamine agonists and similar agents (table 1) can acutely suppress thyrotropin levels to lower-than-normal but detectable values.[3] In patients with true hyperthyroidism, thyrotropin levels are often undetectable. Amphetamines also transiently increase dopamine release for between 1 and 3 weeks. Although atypical antipsychotic agents (such as quetiapine fumarate) possess dopamine-blocking effects, no changes in thyrotropin levels have been reported. Patients who are taking these medications over long periods do not have sustained reductions in thyrotropin levels, and hyperthyroidism does not develop. Similarly, dopamine antagonists, such as metoclopramide hydrochloride, at doses of greater than 1 mg/kg each, can produce slight elevations in thyrotropin levels but not usually greater than 10 mIU/L.

DISPLACEMENT OF THYROID HORMONES FROM THYROID-BINDING GLOBULIN

Clinicians should be aware of medications (for example, nonsteroidal anti-inflammatory drugs[4]) that can displace

Table 1 *Medications that alter thyroid function test results in euthyroid people*

	Laboratory findings			
	Decreased TSH (below normal butdetectable	Increased TSH (usually <10 U/L)	Increased Free T_4	Decreased Free T_4
Medications	Dopamine, levodopa, bromocriptine, glucocorticoids (>0.5 mg/day dexamethasone, 100 mg/day hydrocortisone), octreotide, amphetamines	Metoclopramide >1 mg/kg amiodarone, iodinated contrast media	IV furosemide >80 mg/day, nonsteroidal agents (salicylates >2 g/day, salsalate >1.5-3 g/day, diclofenac, naproxen), IV heparin, amiodarone, iodinated contrast media	Phenytoin, carbamazepine

TSH = thyroid-stimulating hormone (thyrotropin); FT_4 = free thyroxine; IV = intravenous.

thyroid hormones from thyroid-binding globulin and transiently elevate FT_4 and FT_3 concentrations and depress thyrotropin levels (table 1). During continued medication administration, however, FT_4, FT_3, and thyrotropin levels return to normal.

The use of heparin increases lipoprotein lipase activity and produces a fivefold increase in FT_4 levels because T_4 is displaced by free fatty acids. Therefore, to avoid laboratory interference with the test results, FT_4 levels should be measured 1 hour or more after intravenous administration or 10 hours or more after administering low-molecular-weight heparin.[5]

A phenomenon that has confused clinicians for decades is that therapeutic levels of phenytoin and carbamazepine produce sustained reductions in T_4 and FT_3 levels despite normal thyrotropin levels in a clinically euthyroid patient. These paradoxic findings are caused by interference of these agents with the FT_4 assay, producing an underestimation of the FT_4 concentrations.[6] Therefore, clinicians should rely on the thyrotropin level rather than the FT_4 level when assessing thyroid status in patients receiving these agents.

INHIBITION OF CONVERSION OF T_4 TO T_3

Most T_3 is produced from the peripheral conversion of T_4 to T_3 by the enyzme 5-deiodinase. Amiodarone and iodinated contrast media (for example, ipodate, iopanoic acid, and tyropanoate) can inhibit the conversion of T_4 to T_3 both in the peripheral circulation and in the pituitary gland, and can produce confusing thyroid function abnormalities (table 1 and table 2). Within 1 week of ipodate administration, elevations in FT_4 levels, reductions in total T_3 levels, and a transient rise in thyrotropin levels occur; these return to normal within 2 weeks. Similar findings are observed during the first week of amiodarone administration. A transient elevation in thyrotropin levels (<10 mIU/L) occurs during the first 3 months of amiodarone treatment but during ongoing therapy, elevations in FT_4 and reductions in T_3 levels persist in patients who are euthyroid. Therefore, normal FT_4 and T_3 levels in a patient taking amiodarone are highly suggestive of overt thyroid dysfunction.

Beta blockers and corticosteroids that only inhibit the peripheral conversion of T_4 to T_3 interfere minimally with thyroid function test results. Propranolol hydrochloride (>160 mg/d), atenolol, and metoprolol tartrate produce small reductions in total T_3 levels. Large doses of corticosteroids (for example, >4 mg dexamethasone) produce reductions in total T_3 levels, which are useful in the management of thyroid storm or severe hyperthyroidism.

DRUG-INDUCED THYROID DISEASE

Drug-induced thyroid illness is associated with the use of iodides, iodide-containing preparations, lithium, and interferon alpha treatment.[7-10] Routine monitoring of thyroid function tests at baseline and every 3 to 6 months thereafter is recommended in susceptible people (for example, those with thyroid antibodies or euthyroid goiter) receiving these medications.

Iodides

Iodides are hidden in many preparations, including prescription (for example, amiodarone, radiocontrast dyes, povidone iodine, and iodinated glycerol) and nonprescription items (for example, cough and cold preparations, kelp tablets, herbal preparations, and dietary supplements).[5,6] Amiodarone contains 37.5% iodine by weight, exposing patients to an iodine load that is at least 100 times the normal daily intake of 0.5 mg. A dietary supplement, Cellasene (Rexall Sundown, Boca Raton, FL) recently

Table 2 *Effects of amiodarone on thyroid function*

Euthyroid	Hyperthyroidism	Hypothyroidism
↑FT_4 ↑TSH <10 mU/L (transient) ↓Total T_3	↑FT_4 ↑Total T_3 ↓TSH (undetectable levels Antithyroid antibody ±	↓FT_4 ↓Total T_3 ↑TSH >10 mU/L + Antithyroid antibody

FT_4 = free thyroxine; TSH = thyroid-stimulating hormone (thyrotropin); T_3 = triiodothyronine.

promoted to reduce cellulite, was found to contain 930 µg of iodine per recommended dose of three capsules. Thyroid dysfunction has been reported after the vaginal use of povidone iodine.[6] As much as 175 mg of iodide can be released from radiographic contrast media.

Iodide-induced hyperthyroidism (Jod-Basedow disease) usually develops within 3 to 8 weeks after an increase in iodide supplementation (for example, after the administration of radiocontrast dye or amiodarone) in persons with autonomously functioning, nontoxic multinodular goiters. Hyperthyroid symptoms can persist for several months, requiring therapy with thioamides and beta blockers. Radioactive iodine is not effective because the iodine loading prevents effective retention of the radioactive iodine. Iodide-induced hyperthyroidism has been attributed to malfunction of the Wolff-Chaikoff block.[5] This autoregulatory block normally protects the gland against excessive hormone production and the development of hyperthyroidism once a critical intrathyroidal iodide concentration is achieved.

Iodide-induced hypothyroidism is most common, but goiter and hyperthyroidism also occur. Risk factors for drug-induced hypothyroidism in people who are not taking thyroid supplements are listed in the box below. Women are at greater risk than men, as are those who show thyroid antibodies before starting therapy. Iodide-induced hypothyroidism develops if the gland is unable to "escape" from the Wolff-Chaikoff block after several days to resume normal hormone production. Thyroxine therapy should be administered for at least 6 months before attempts to stop are considered.

Amiodarone is being increasingly used for the management of a number of cardiac conditions, including atrial fibrillation and congestive heart failure. The overall prevalence of amiodarone-induced thyroid disease is estimated to be 2% to 24%.[11] Hypothyroidism is more common than hyperthyroidism. No clear relation exists between the development of thyroid dysfunction and either the cumulative dosage or the duration of amiodarone therapy, although most cases develop within the first 2 years of therapy. Rarely, because of amiodarone's long half-life (40-55 days) and sequestration in adipose tissue, thyroid dysfunction can occur the first year after it is stopped.

Some risk factors for drug-induced hypothyroidism in people not taking thyroid supplements

- Autoimmune thyroiditis (such as Hashimoto disease)
- Previous thyroid disease
- Partial thyroidectomy
- History of radioactive iodine administration
- History of postpartum thyroid disease
- Family history of thyroid disease
- Previous thyroid damage
- Female sex
- Preexisting or de novo development of antithyroid antibodies

Hypothyroidism is reported in 6% to 10% of patients receiving amiodarone and may be difficult to recognize because bradycardia and constipation are also common side effects of amiodarone use. Hypothyroidism should be confirmed by thyroid function tests (table 2). Levothyroxine replacement is often necessary even if amiodarone is stopped or the dosage reduced. After 1 year, thyroxine supplementation can be stopped to evaluate the need for continued therapy. Few guidelines are available for regulating thyroxine replacement. A return of the thyrotropin level to normal might not be possible without aggravating the underlying cardiac status. If amiodarone therapy is continued, thyroxine replacement should be maintained indefinitely.

Hyperthyroidism is reported in 1% to 5% of patients. The typical signs and symptoms are often not apparent, and clinical suggestions of hyperthyroidism should be confirmed by laboratory findings (table 2). Cardiac symptoms, weight loss, tremor, sleep disturbances, and myopathy could be attributed to amiodarone use, the existing cardiac disease, or hyperthyroidism. Two types of amiodarone-induced hyperthyroidism have been identified. Type 1 is a Graves disease-like hyperthyroidism, characterized by the presence of antithyroid antibodies. Type 2 is a subacute thyroiditis (no antithyroid antibodies) that is caused by a direct toxic effect on the gland, producing a "dumping" of thyroid hormone into the circulation.[7,12] Treatment is complicated, and referral to an endocrinologist is recommended. Treatment is necessary even after amiodarone is stopped because the hyperthyroidism can persist for several months due to amiodarone's long duration of action.

Lithium

Hypothyroidism and subclinical hypothyroidism have been reported in 5% to 20% and as high as 50% of people taking lithium carbonate.[3,9,10,13] A smooth, nontender goiter is observed in up to 60% of those receiving lithium for 5 months to 2 years; hypothyroidism may not be present.

As with iodides, lithium is concentrated in the gland and interferes with thyroid hormone synthesis and release, causing a compensatory increase in thyrotropin levels. A twofold increase in the incidence of thyroid antibodies has been found in patients treated with lithium (24%) compared with those not taking lithium (12%). The risk of lithium-induced antibodies increases with the duration of therapy (for example, >2 years) and is more common in women than in men. Antibody titers increased in two thirds of people with thyroid antibodies at baseline.[13,14]

Lithium-induced hypothyroidism is more frequent in those taking lithium for more than 2 years. Close moni-

toring of thyrotropin levels, rather than the immediate institution of thyroxine therapy, is reasonable in patients with subclinical hypothyroidism induced by lithium because abnormal thyrotropin levels can return to normal spontaneously. In a review of several prospective studies, a substantial fall in serum hormone levels and a rise in thyrotropin levels within 10 days to a few months of starting therapy were reported.[14] The thyroid abnormalities, however, returned to pretreatment levels within the first year, without additional therapy or interruptions or changes in lithium therapy. Thyrotropin levels were less likely to return to normal in people with preexisting antithyroid antibodies.

Levothyroxine supplementation can reverse the hypothyroidism, prevent further growth of an existing goiter, and permit the continued administration of lithium. Once lithium is stopped, the goiter and hypothyroidism do not always resolve. Management with thioamides should be considered, as should the surgical removal of the goiter.

Interferon alpha

Thyroid dysfunction is common after interferon alpha therapy for chemotherapy or long-term treatment of hepatitis C.[15-17] In contrast, thyroid dysfunction after the administration of interferon beta-1b for the treatment of multiple sclerosis is rare.[18]

The prevalence of thyroid abnormalities during interferon therapy ranges from 2.5% to 20%.[15,16] Symptoms of thyroid dysfunction may be absent or occur as early as 6 to 8 weeks after starting therapy or be delayed until after 6 to 23 months of receiving therapy. Hypothyroidism is more common (40%-50% of patients) than hyperthyroidism (10%-30% of patients). Fortunately, thyroid dysfunction seems to be transient in most patients, and treatment is not always necessary. Levothyroxine treatment is necessary only to alleviate hypothyroid symptoms; hypothyroidism often resolves spontaneously within 2 to 3 months after stopping therapy. Similarly, beta-blockade therapy is only needed for symptomatic hyperthyroidism because the hyperthyroidism is often transient. Thyroid dysfunction may take as long as 17 months after stopping therapy to resolve. Thyroid disease is rarely permanent.

MEDICATIONS THAT AFFECT T_4 REQUIREMENTS

Thyroid hormones are metabolized primarily by deiodination, but glucuronidation and sulfation are also important routes of elimination. Cytochrome P-450 hepatic enzyme inducers (for example, rifampin, rifabutin, phenytoin, carbamazepine, and phenobarbital) can increase the metabolic elimination of T_4 and T_3 by 20%, which is not clinically important in people who are euthyroid. Those requiring thyroxine replacement therapy, however, may need higher doses to maintain euthyroidism. Ritonavir, a potent P-450 mixed hepatic enzyme inhibitor and inducer, can increase thyroxine glucuronidation, necessitating a twofold increase in thyroxine dosage to maintain euthyroidism.[19]

Serotonin reuptake inhibitors may also alter T_4 requirements. In nine patients receiving thyroxine therapy, an elevation in thyrotropin levels and a reduction in FT_4 levels were noted after the addition of sertraline hydrochloride.[20] An increase in thyroxine clearance was thought to have occurred.

DRUGS THAT IMPAIR THE ABSORPTION OF EXOGENOUS THYROXINE

Patients should take levothyroxine on an empty stomach for optimal absorption. Several medications, including iron, aluminum-containing products (such as sucralfate, antacids, and didanosine), sodium polystyrene sulfonate, resin binders, and calcium carbonate have been reported to impair the absorption of exogenous thyroxine and decrease its efficacy.[21-24]

Not all calcium carbonate preparations have been implicated. Patients should take levothyroxine at least 4 hours before or after taking any medication that might interfere with absorption to minimize this interaction. To maintain euthyroidism, the levothyroxine dosage may need to be adjusted or the offending agent stopped.

CONCLUSIONS

The accurate interpretation of abnormal thyroid function test results may be complicated by the concomitant presence of medications and nonthyroidal illnesses. It is important that clinicians recognize the effects of drugs on laboratory interpretation, drug-induced thyroid illnesses, and exogenous thyroid requirements to prevent medical treatments that may be dangerous or that inappropriately increase the cost of caring for patients.

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Scientific Jargon

by Dyrk Schingman
Oregon State University

After several years of studying and hard work, I have finally learned scientific jargon. The following list of phrases and their definitions will help you to understand that mysterious language of science and medicine.

Scientific Phrase	Translation
"It has long been known"	I didn't look up the original reference.
"A definite trend is evident"	These data are practically meaningless.
"While it has not been possible to provide definite answers to the questions"	An unsuccessful experiment, but I still hope to get it published.
"Three of the samples were chosen for detailed study"	The other results didn't make any sense.
"Typical results are shown"	This is the prettiest graph.
"These results will be in a subsequent report"	I might get around to this sometime, if pushed/funded.
"The most reliable results are obtained by Jones"	He was my graduate student; his grade depended on this.
"In my experience"	Once.
"In case after case"	Twice.
"In a series of cases"	Thrice.
"It is believed that"	I think.
"It is generally believed that"	A couple of other guys think so too.
"Correct within an order of magnitude"	Wrong.
"According to statistical analysis"	Rumor has it.
"A statistically oriented projection of the significance of these findings"	A wild guess.
"A careful analysis of obtainable data"	Three pages of notes were obliterated when I knocked over a glass of beer.
"It is clear that much additional work will be required before a complete understanding of this phenomena occurs"	I don't understand it.
"After additional study by my colleagues"	They don't understand it either.
"Thanks are due to Joe Blotz for assistance with the experiment and to Andrea Schaeffer for valuable discussions"	Mr. Blotz did the work and Ms. Shaeffer explained to me what it meant.
"A highly significant area for exploratory study"	A totally useless topic selected by my committee.
"It is hoped that this study will stimulate further investigation in this field"	I quit.