REVIEW ARTICLE

DRUG THERAPY

ALASTAIR J.J. WOOD, M.D., *Editor*

DRUGS AND THYROID FUNCTION

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TESTING of thyroid function is common in clinical practice. Many patients who are tested, including those who have or are receiving treatment for thyroid disease, take medications that may affect thyroid function. Therefore, the possible effect of these drugs both on the results of thyroid-function tests and on the effectiveness of treatment must always be considered in decisions regarding patient care.

The pathways of thyroid hormone synthesis, secretion, transport in the circulation, and metabolism offer numerous targets for drug interaction (Fig. 1 and 2). Normal thyroid secretion depends on thyrotropin (TSH). Secretion of TSH is, in turn, inhibited by thyroid hormones and stimulated by thyrotropin-releasing hormone (TRH). Iodide in serum is trapped by thyroid cells, after which it is oxidized and incorporated into some of the tyrosine residues of thyroglobulin, which then couple to form thyroxine (T_4) and triiodothyronine (T_3).

The thyroid gland normally contains large stores of thyroglobulin, most of which is in the lumen of the thyroid follicles. When thyroglobulin is resorbed into the follicular cells of the thyroid and hydrolyzed, T_4 and T_3 are secreted into the circulation. There they are bound to specific serum-binding proteins, so that very little circulates as free T_4 or T_3. In extrathyroidal tissues, T_4 is converted to T_3 by the action of several T_4 5′-deiodinases; this process generates about 80 percent of the circulating T_3. About 80 percent of T_4 and T_3 is metabolized by deiodination and 20 percent by non-deiodinative pathways that include conjugation with glucuronides and sulfates, decarboxylation, and deamination.[1] In tissues, T_3 and — to a much smaller extent — T_4 are bound to specific nuclear receptor proteins that interact with regulatory regions of genes, influencing their expression.

In this paper we shall discuss the effects of groups of drugs on the production, secretion, transport, and metabolism of T_4 and T_3 and on the absorption of exogenously administered T_4.

DRUGS AFFECTING THE SECRETION OF TSH

Measurement of serum TSH is the single best test of thyroid function, because of the sensitivity of TSH secretion to very small changes in serum T_4 and T_3 concentrations. Serum TSH concentrations are low in patients with hyperthyroidism and high in those with primary hypothyroidism. When hypothyroidism results from hypothalamic or pituitary disease, serum TSH values are usually low or normal, but occasionally they are high because of the secretion of biologically inactive TSH.[2,3]

Several drugs decrease TSH secretion and lower serum TSH concentrations, although not to values as low as those found in patients with hyperthyroidism (Table 1). These agents are dopamine (in doses of at least 1 μg per kilogram of body weight per minute),[4-8] glucocorticoids (e.g., dexamethasone, in doses of 0.5 mg or more per day or hydrocortisone in doses of 100 mg or more per day),[9,10] and octreotide (in doses of more than 100 μg per day), which is a somatostatin analogue used for the treatment of acromegaly and certain other hormone-excess syndromes.[11,12] Patients who are receiving long-term glucocorticoid or octreotide therapy do not, however, have sustained reductions in TSH secretion, nor does hypothyroidism develop, probably because of the effect of decreased thyroid hormone secretion in increasing TSH secretion. Patients who require infusions of dopamine for more than a few days may have reductions in secretion by the thyroid, which are difficult to distinguish from the changes in serum T_4 and T_3 concentrations that result from the underlying illness.

DRUGS AFFECTING THE SECRETION OF THYROID HORMONE

In addition to methimazole and propylthiouracil, which are given deliberately to decrease thyroid hormone production in patients with hyperthyroidism, several other commonly used drugs may decrease thyroid hormone secretion. These include lithium carbonate and iodine-containing medications (Table 1).

Drugs That Cause Hypothyroidism

Lithium interferes with thyroid hormone synthesis and decreases thyroid hormone secretion. Long-term lithium treatment results in goiter in up to 50 percent of patients, subclinical hypothyroidism in up to 20 percent, and overt hypothyroidism in up to 20 percent.[13-15] Many lithium-treated patients have antithyroid antibodies in their serum; among them about 50 percent have subclinical hypothyroidism, as compared with 15 percent of patients with no antithyroid antibodies.[15] The antithyroid antibodies probably indicate the presence of preexisting chronic autoimmune thyroiditis, which would be expected to increase sensitivity to the antithyroid actions of lithium, but which could, alternatively, be induced by lithium.

Normal subjects given 1 to 2 mg of inorganic iodide per day (in addition to their usual diet) have a transient decrease in T_4 and T_3 secretion and a transient increase in TSH secretion.[16] The decrease in T_4 and T_3 secretion is much greater, but is usually also transient, in patients with hyperthyroidism.[17] However, in patients with chron-

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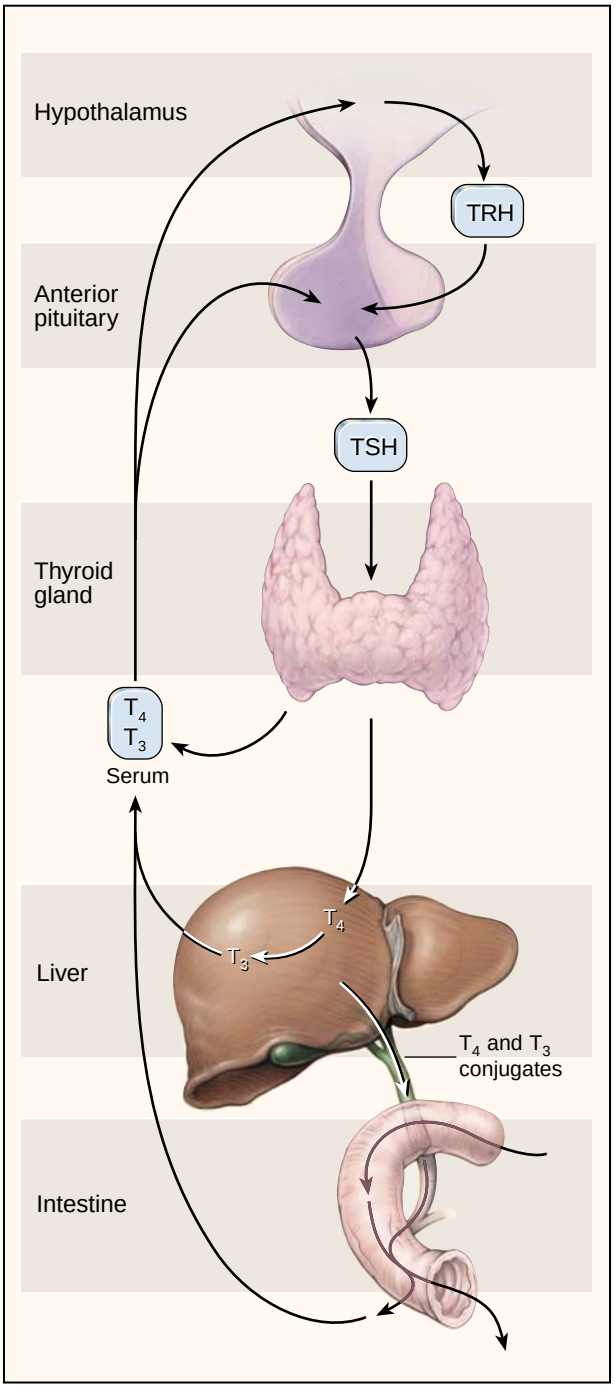

Figure 1. The Hypothalamic–Pituitary–Thyroid Axis and Extrathyroidal Pathways of Thyroid Hormone Metabolism.

Triiodothyronine (T_3) and thyroxine (T_4) inhibit the secretion of thyrotropin (TSH) both directly and indirectly, by inhibiting the secretion of thyrotropin-releasing hormone (TRH). TSH stimulates the synthesis and secretion of T_4 and T_3 by the thyroid gland. T_4 is converted to T_3 in the liver (and many other tissues) by the action of T_4 monodeiodinases. Some of the T_4 and T_3 is conjugated with glucuronide and sulfate in the liver, excreted in the bile, and partially hydrolyzed in the intestine; the T_4 and T_3 formed there may be reabsorbed. Drug interactions can occur at any of these sites.

ic autoimmune thyroiditis, in patients with hyperthyroidism who have received radioactive iodine therapy or have undergone partial thyroidectomy, and probably in patients whose thyroid gland is damaged in any other way, iodide may induce persistent hypothyroidism.[16] In these patients, unlike normal subjects and previously untreated patients with hyperthyroidism, adaptation to the antithyroid action of iodide does not occur.

In addition to inorganic iodide, there are many iodine-containing organic compounds used in clinical practice that are partially deiodinated in vivo and therefore can affect thyroid function (Table 2). The risks posed by the use of radiographic contrast agents for coronary angiography or computed tomography is of particular concern because of the widespread use of these procedures. The contrast agents usually are given in doses of 100 to 150 ml for diagnostic testing and up to 400 to 500 ml when coronary angioplasty is also performed. Even though the parent compounds are excreted in 10 to 14 days, minimal deiodination (e.g., only 0.1 percent) will result in the release of as much as 14 to 175 mg of iodide. Oral cholecystographic agents and amiodarone, especially, are much more slowly excreted and may cause more prolonged hypothyroidism.

Several other drugs have been reported to cause hypothyroidism. Long-term treatment with aminoglutethimide results in small decreases in serum T_4 and T_3 concentrations and increases in serum TSH concentrations, although all the values remain within the normal range in most patients.[18,19] Many other drugs, such as tolbutamide and the sulfonamides, have been reported to cause hypothyroidism in occasional patients, but a direct cause-and-effect relation has rarely been proved.[20]

Drugs That Cause Hyperthyroidism

Iodide and drugs that contain pharmacologic amounts of iodide (Table 2) may also cause hyperthyroidism in euthyroid patients with thyroid autonomy — that is, multinodular goiter or hyperfunctioning thyroid adenoma — and in patients with these disorders and also Graves' disease who live in areas of severe iodine deficiency.[16,21,22] The hyperthyroidism may develop within three to eight weeks after iodine or drug administration and may persist for several months after therapy is discontinued. Amiodarone may also induce hyperthyroidism by causing thyroiditis.[23]

Drugs Affecting T_4 Absorption

The gastrointestinal tract has a role in thyroid physiology because T_4 and T_3 conjugates are excreted in the bile and partially deconjugated in the intestine, releasing small amounts of T_4 and T_3 for reabsorption. A very small portion of the daily production of T_4 and T_3, less than 10 percent, is excreted in the stool.[24] In people with normal thyroid function, this pathway of T_4 and T_3 recirculation contributes so little to hormone availability that patients who have gastrointestinal disease or are receiving drugs that decrease T_4 absorption do not have abnormal thyroid function.

In patients receiving oral T_4, however, the situation is

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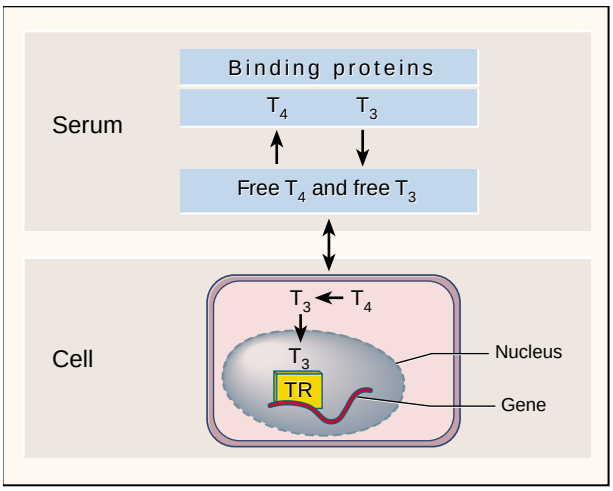

Figure 2. Thyroid Hormone Transport in Serum and Hormone Action.

The binding proteins include thyroxine-binding globulin, transthyretin, and albumin. Drugs may alter the production or clearance of a binding protein or inhibit the binding of thyroxine (T_4) and triiodothyronine (T_3) to the protein. TR denotes thyroid receptor.

different. Normally, about 80 percent of a usual dose (50 to 150 μg per day) is absorbed, mostly in the jejunum and the upper part of the ileum. In patients who are dependent on exogenous T_4, drugs that decrease T_4 absorption may induce hypothyroidism (Table 1). Among untreated patients, the severity of hypothyroidism might be expected to increase.

The bile acid sequestrants colestipol and cholestyramine bind T_4 and decrease its absorption, and they have proved useful in the treatment of patients with exogenous hyperthyroidism.[25] A decrease in serum T_4 concentrations and an increase in serum TSH concentrations occurred when cholestyramine was administered to T_4-treated patients with hypothyroidism.[26] In normal subjects, thyroid function is not affected by these drugs.[27]

Decreased absorption of T_4 and increases in serum TSH concentrations have also been reported in T_4-treated patients with hypothyroidism who are given aluminum hydroxide,[28,29] ferrous sulfate,[30] or sucralfate,[31] but absorption of T_4 was not decreased in the majority of the patients treated with ferrous sulfate and sucralfate who were studied.[30,32,33] The interactions can be minimized by having the patient take T_4 and the other drug several hours apart. Therefore, even though interference with T_4 absorption seems to occur in relatively few patients, it is prudent to advise all patients to take their T_4 and other medications at different times.

Drugs Affecting T_4 and T_3 Transport in Serum

More than 99 percent of the T_4 and T_3 in serum is bound to one of the three major transport proteins: thyroxine-binding globulin (TBG), transthyretin, and albumin.[34,35] TBG binds approximately 70 percent of serum T_4 and a larger fraction of serum T_3; it is therefore the most important of the binding proteins. Although less than 0.1 percent of T_4 and T_3 circulates unbound to proteins, it is the concentration of free hormone that determines the action of the hormones in tissues. Alterations in the serum concentrations of these binding proteins alter serum total T_4 and T_3 concentrations, but not serum concentrations of free T_4 and T_3; therefore the patient remains euthyroid. Drugs may affect T_4 and T_3 transport either by raising or lowering the serum concentration of a binding protein or by interfering with the binding of T_4 and T_3 to a binding protein. Nearly all the drugs that alter T_4 and T_3 transport do so by altering the serum concentration of TBG or its affinity for T_4 and T_3.

Increases in Serum TBG Concentrations

The most common causes of an increase in serum TBG concentrations are an increase in estrogen production and the administration of estrogen, either as a component of an oral contraceptive agent or as estrogen-replacement therapy (Table 1).[36-40] TBG is a glycoprotein that is synthesized in the liver. Estrogens produce increased sialylation of TBG, which decreases its rate of clearance and raises its serum concentration.[35] The increase in TBG in serum is dose-dependent. The usual doses of ethinyl estradiol (20 to 35 μg per day) and conjugated estrogen (0.625 mg per day) raise serum TBG concentrations by approximately 30 to 50 percent and serum T_4 concentrations by 20 to 35 percent.[36-40] The increases begin within two weeks, and a new steady state is attained in four to eight weeks. In women with hypothyroidism who are receiving T_4 and become pregnant, an increase of 45 percent in the dose is needed, on average, to maintain normal serum TSH concentrations.[41] Thus, the increase in serum total T_4 concentrations induced by estrogen occurs as a result of at least a transient increase in T_4 secretion.

Addition of a progestogen to estrogen therapy does not alter the estrogen-induced increase in the serum TBG concentrations, and progesterone alone has no effect. Oral estrogen has a first-pass effect on the liver; transdermal administration of estrogen does not raise serum TBG or T_4 concentrations, even though serum estrogen concentrations are comparable to those measured after oral administration.[37] Tamoxifen has weak estrogen-agonist effects in the liver and raises serum TBG concentrations slightly.[42]

Serum TBG concentrations are increased in about 50 percent of patients who use heroin for long periods or are treated with methadone.[43-45] Many of these patients also have abnormal liver function, so that the increase in serum TBG may result from liver disease rather than from specific effects of these drugs.[43,44] Cocaine use has not been associated with changes in serum TBG, T_4, or T_3 concentrations.[46]

Mitotane and fluorouracil are also associated with increases in serum concentrations of total T_4 and T_3, but serum free T_4 and TSH concentrations remain nor-

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Table 1. Drugs That Influence Thyroid Function.*

Drugs that decrease TSH secretion
Dopamine
Glucocorticoids
Octreotide
Drugs that alter thyroid hormone secretion
Decreased thyroid hormone secretion
Lithium
Iodide
Amiodarone
Aminoglutethimide
Increased thyroid hormone secretion
Iodide
Amiodarone
Drugs that decrease T_4 absorption
Colestipol
Cholestyramine
Aluminum hydroxide
Ferrous sulfate
Sucralfate
Drugs that alter T_4 and T_3 transport in serum
Increased serum TBG concentration
Estrogens
Tamoxifen
Heroin
Methadone
Mitotane
Fluorouracil
Decreased serum TBG concentration
Androgens
Anabolic steroids (e.g., danazol)
Slow-release nicotinic acid
Glucocorticoids
Displacement from protein-binding sites
Furosemide
Fenclofenac
Mefenamic acid
Salicylates
Drugs that alter T_4 and T_3 metabolism
Increased hepatic metabolism
Phenobarbital
Rifampin
Phenytoin
Carbamazepine
Decreased T_4 5′-deiodinase activity
Propylthiouracil
Amiodarone
Beta-adrenergic–antagonist drugs
Glucocorticoids
Cytokines
Interferon alfa
Interleukin-2

*TSH denotes thyrotropin, T_4 thyroxine, T_3 triiodothyronine, and TBG thyroxine-binding globulin.

mal.[47,48] It is likely that these drugs also increase the serum concentration of TBG.

Decreases in Serum TBG Concentrations

In contrast to those treated with estrogens, patients taking androgens or anabolic steroids have decreased serum TBG and T_4 concentrations (Table 1).[49-51] These patients are clinically euthyroid, their serum free T_4 and TSH concentrations remain within the normal range, and their production and turnover of T_4 are normal. The administration of androgen to women with breast cancer who also had hypothyroidism and were being treated with T_4 induced hyperthyroidism, with an increase in serum free T_4 and a decrease in serum TSH concentrations.[52] These results suggest that androgens not only lower serum TBG concentrations but also slightly decrease T_4 production. A decrease in the serum TBG concentration also occurs during long-term glucocorticoid treatment.

Patients treated with nicotinic acid may have decreased serum TBG and T_4 concentrations.[53-55] In one study, treatment of hypercholesterolemia with colestipol and niacin (3 to 6 g per day) resulted in a 25 percent decrease in the serum TBG concentration and a small decrease in the serum T_4 concentration (1.5 μg per deciliter [1.9 nmol per liter])[53] but no change in the serum free T_4 and TSH concentrations. The changes were probably caused by the niacin, since colestipol alone has no effect on thyroid function.[27]

Inhibition of the Binding of T_4 and T_3 to TBG

At therapeutic concentrations, several drugs inhibit the binding of T_4 and T_3 to TBG to varying degrees (Table 1). The initial effect of these drugs is to increase serum free T_4 concentrations, because the drug displaces T_4 from TBG; continued administration, however, results in a decrease in serum T_4, normal serum free T_4, and normal serum TSH concentrations.

Furosemide has no effect at the usual therapeutic concentrations, but large intravenous doses (more than 80 mg) result in a transient increase in serum free T_4 concentrations and a decrease in serum total T_4 concentrations.[56-58] The changes in serum total and free T_4 vary depending on the length of time between the administration of the drug and the collection of the sam-

Table 2. Iodine Content of Some Iodine-Containing Medications and Radiographic Contrast Agents.

Substance	Amount of Iodine
Expectorants	
Iophen	25 mg/ml
Organidin (iodinated glycerol)	15 mg/tablet
Par Glycerol	5 mg/ml
R-Gen	6 mg/ml
Iodides	
Potassium iodide (saturated solution)	~25 mg/drop
Pima syrup (potassium iodide)	255 mg/ml
Lugol's solution (potassium iodide + iodine)	~7 mg/drop
Iodo-Niacin	115 mg/tablet
Antiasthmatic drugs	
Mudrane	195 mg/tablet
Elixophyllin-KI (theophylline) elixir	6.6 mg/ml
Iophylline	2 mg/ml
Antiarrhythmic drugs	
Amiodarone	75 mg/tablet
Antiamebic drugs	
Iodoquinol	134 mg/tablet
Topical antiseptic agents	
Povidone–iodine	10 mg/ml
Clioquinol cream	12 mg/g
Douches	
Povidone–iodine	10 mg/ml
Radiographic contrast agents	
Iopanoic acid	333 mg/tablet
Ipodate sodium	308 mg/tablet
Intravenous preparations	140–380 mg/ml

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ple, on the rate of renal clearance of the drug, and on the serum concentrations of albumin (which also binds furosemide) and TBG. Several nonsteroidal antiinflammatory drugs have similar effects.[57]

Salicylates (in doses of >2.0 g per day) and salsalate (in doses of 1.5 to 3.0 g per day) also inhibit the binding of T_4 and T_3 to TBG; salicylates inhibit binding to transthyretin as well.[59] As with furosemide, the initial effect is an increase in serum free T_4 concentrations.[60] When therapeutic serum concentrations are sustained, salicylates result in a 20 to 30 percent decrease in serum total T_4 concentrations and normal serum free T_4 concentrations. Salsalate may result in a greater decrease in the serum T_4 concentration (by 30 to 40 percent) and a decrease in the serum free T_4 index,[61-63] but the latter change is probably an in vitro artifact.[60]

Serum free T_4 concentrations increase transiently after the administration of heparin.[64] This increase is caused in vitro by the inhibition of protein binding of T_4 by the free fatty acids generated as a result of the ability of heparin to activate lipoprotein lipase.[65-67]

Metabolism of T_4 and T_3

T_4 and T_3 are metabolized mostly by deiodination but also by glucuronidation and sulfation.[1,68] The activity of the enzymes that facilitate these reactions is affected by a variety of drugs (Table 1). Their actions, in general, vary according to whether the patient has normal pituitary–thyroid function and therefore can compensate for any alteration in T_4 and T_3 metabolism or has hypothyroidism and therefore little ability to increase whatever thyroid secretion persists. Among these drugs are phenobarbital and rifampin,[68-71] which increase T_4 and T_3 metabolism by stimulating hepatic microsomal drug-metabolizing enzyme activity. Hypothyroid patients treated with T_4 may become hypothyroid again when rifampin is administered.[71]

Phenytoin and carbamazepine have more complex effects. Like phenobarbital and rifampin, the two anticonvulsant drugs increase the rate of T_4 and T_3 metabolism and can cause hypothyroidism in patients with hypothyroidism who are treated with T_4.[72] Phenytoin and carbamazepine also cause a decrease of 20 to 40 percent in serum total and free T_4 concentrations and a smaller decrease in serum total and free T_3 concentrations in patients who have no thyroid disease[73-76]; most have normal serum TSH concentrations, are clinically euthyroid, and have a normal resting metabolic rate.[73,77] These paradoxical findings, notably the decrease in serum free T_4 and T_3 concentrations in the absence of any other evidence of hypothyroidism, may be explained by recent measurements of free T_4 in undiluted human serum by ultrafiltration (Surks MI, DeFesi CR: unpublished data). In these assays, in contrast to previous measurements in which serum was diluted, serum free T_4 concentrations were normal in patients treated with phenytoin and carbamazepine. Transient hypothyroidism has been reported in a few patients with hypersensitivity reactions to phenytoin.[20]

T_4 5′-Deiodinase

Most of the T_3 produced outside the thyroid results from the action of the T_4 5′-deiodinase (type I) that is found mainly in liver, kidney, and muscle.[1,68] Drugs that inhibit this enzyme result in a decrease in T_3 production and lower serum T_3 concentrations (Table 1). Occasionally, serum T_4 concentrations increase as well.

Although amiodarone may cause either hypothyroidism or hyperthyroidism, most patients treated with amiodarone remain euthyroid but have altered serum T_4 and T_3 concentrations.[21,78] Their serum total and free T_4 concentrations increase to the high-normal range or just above normal, and their serum T_3 concentrations decrease to low-normal. Serum TSH concentrations remain normal, although occasionally they are slightly high during the first several months of treatment.

Small decreases in serum T_3 concentrations occur in patients treated with large doses (>160 mg per day) of propranolol, and a few have small increases in serum T_4 concentrations.[79,80] The patients are clinically euthyroid and have normal serum TSH concentrations. Among patients with hyperthyroidism, atenolol, alprenolol, and metoprolol decrease serum T_3 concentrations slightly, but serum T_4 concentrations do not change.[81,82]

Large doses of glucocorticoids — for example, 4 mg of dexamethasone per day — also cause a 30 percent decrease in serum T_3 concentrations within several days.[83-87] There is minimal short-term change in serum T_4 concentrations, but, as noted above, they may decline slightly during long-term glucocorticoid therapy because of decreased production of TBG.

Thyroid Dysfunction Caused by Cytokines

Thyroid dysfunction may develop in patients with chronic inflammatory disorders or tumors who receive long-term treatment with cytokines. Therapy with interferon alfa is associated with the development of antithyroid microsomal (antithyroperoxidase) antibodies in 20 percent of patients, and some have transient hyperthyroidism, hypothyroidism, or both.[88-90] Patients who have antithyroid antibodies before treatment are at higher risk for thyroid dysfunction during treatment. Thyroid dysfunction has not been reported during treatment with interferon beta or gamma.[91,92] Therapy with interleukin-2 was associated with transient painless thyroiditis in about 20 percent of patients.[93,94]

Conclusions

Drugs can affect thyroid economy in numerous ways. They may cause hyperthyroidism or hypothyroidism, subclinical or overt hypothyroidism in patients treated with T_4, or abnormalities on any of the tests used to evaluate patients in whom thyroid dysfunction is suspected. Knowledge of the site of drug interaction and the physiologic features of the thyroid hormone system should enable the clinician to anticipate these changes.

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