## Chapter 20: Thyroid Disorders

# INTRODUCTION

- *Thyroid disorders* involve thyroid hormone production or secretion and result in alterations in metabolic stability.

# THYROID HORMONE PHYSIOLOGY

- The thyroid hormones thyroxine ($T_4$) and triiodothyronine ($T_3$) are formed within thyroglobulin, a large glycoprotein synthesized in the thyroid cell. Inorganic iodide enters the thyroid follicular cell and is oxidized by thyroid peroxidase and covalently bound (organified) to tyrosine residues of thyroglobulin.
- Iodinated tyrosine residues monoiodotyrosine (MIT) and diiodotyrosine (DIT) combine (couple) to form iodothyronines in reactions catalyzed by thyroid peroxidase. Thus, two molecules of DIT combine to form $T_4$, and MIT and DIT join to form $T_3$.
- Proteolysis within thyroid cells releases thyroid hormone into the bloodstream. $T_4$ and $T_3$ are transported by thyroid-binding globulin (TBG), transthyretin, and albumin. Only the unbound (free) thyroid hormone can diffuse into cells, elicit biologic effects, and regulate thyroid-stimulating hormone (TSH) secretion from the pituitary.
- $T_4$ is secreted solely from the thyroid, but <20% of $T_3$ is produced there; most $T_3$ is formed from breakdown of $T_4$ catalyzed by the enzyme 5′-monodeiodinase in peripheral tissues. $T_3$ is five times more active than $T_4$. $T_4$ may also be acted on by 5′-monodeiodinase to form reverse $T_3$, which has no significant biologic activity.
- Thyroid hormone production is regulated by TSH secreted by the anterior pituitary, which in turn is under negative feedback control by the circulating level of free thyroid hormone and the positive influence of hypothalamic thyrotropin-releasing hormone (TRH). Thyroid hormone production is also regulated by extrathyroidal deiodination of $T_4$ to $T_3$, which can be affected by nutrition, nonthyroidal hormones, drugs, and illness.

# THYROTOXICOSIS (HYPERTHYROIDISM): PATHOPHYSIOLOGY

- Thyrotoxicosis results when tissues are exposed to excessive levels of $T_4$, $T_3$, or both. Hyperthyroidism, which is one cause of thyrotoxicosis, refers to overproduction of thyroid hormone by the thyroid gland.
- TSH-secreting pituitary tumors occur sporadically and release biologically active hormone that is unresponsive to normal feedback control. The tumors may cosecrete prolactin or growth hormone; therefore, patients may present with amenorrhea, galactorrhea, or signs of acromegaly.
- Resistance to thyroid hormone occurs rarely and can be due to various molecular defects, including mutations in the TRβ gene. Pituitary resistance to thyroid hormone (PRTH) refers to selective resistance of the pituitary thyrotrophs to thyroid hormone.
- Graves' disease is the most common cause of hyperthyroidism, which results from the action of thyroid-stimulating antibodies (TSAb) directed against the thyrotropin receptor on the surface of thyroid cells. These immunoglobulins bind to the receptor and activate the enzyme adenylate cyclase in the same manner as TSH.
- An autonomous thyroid nodule (toxic adenoma) is a benign thyroid mass that produces thyroid hormone independent of pituitary and TSH control. Hyperthyroidism usually occurs with larger nodules (>3 cm in diameter).

- In multinodular goiter, follicles with autonomous function coexist with normal or even nonfunctioning follicles. Thyrotoxicosis occurs when autonomous follicles generate more thyroid hormone than is required.
- Painful subacute (granulomatous or de Quervain) thyroiditis often develops after a viral syndrome, but rarely has a specific virus been identified in thyroid parenchyma.
- Painless (silent, lymphocytic, or postpartum) thyroiditis is a common cause of thyrotoxicosis. Its etiology is not fully understood; autoimmunity may underlie most cases.
- Thyrotoxicosis factitia is hyperthyroidism due to ingestion of exogenous thyroid hormone. This may occur when thyroid hormone is used for inappropriate indications, excessive doses are used for accepted medical indications, there is accidental ingestion, or it is used surreptitiously.
- Amiodarone may induce thyrotoxicosis (2%–3% of patients), overt hypothyroidism (5% of patients), subclinical hypothyroidism (25% of patients), or euthyroid hyperthyroxinemia. Because of amiodarone's high iodine content (37% by weight), increased thyroid hormone synthesis commonly exacerbates thyroid dysfunction in patients with preexisting thyroid disease. Amiodarone also causes a destructive thyroiditis with leakage of thyroglobulin and thyroid hormones.

## CLINICAL PRESENTATION

- Symptoms of thyrotoxicosis include nervousness, anxiety, palpitations, emotional lability, easy fatigability, heat intolerance, weight loss concurrent with increased appetite, increased frequency of bowel movements, proximal muscle weakness (noted on climbing stairs or arising from a sitting position), and scanty or irregular menses in women.
- Physical signs include warm, smooth, moist skin, and unusually fine hair; separation of the ends of the fingernails from the nail beds (onycholysis); retraction of the eyelids and lagging of the upper lid behind the globe upon downward gaze (lid lag); tachycardia at rest, widened pulse pressure, and systolic ejection murmur; occasional gynecomastia in men; fine tremor of the protruded tongue and outstretched hands; and hyperactive deep tendon reflexes. Thyromegaly is usually present.
- Graves' disease is manifested by hyperthyroidism, diffuse thyroid enlargement, and extrathyroidal findings of exophthalmos, pretibial myxedema, and thyroid acropachy. In severe disease, a thrill may be felt and a systolic bruit may be heard over the gland.
- In subacute thyroiditis, patients have severe pain in the thyroid region, which often extends to the ear. Systemic symptoms include fever, malaise, myalgia, and signs and symptoms of thyrotoxicosis. The thyroid gland is firm and exquisitely tender on physical examination.
- Painless thyroiditis has a triphasic course that mimics painful subacute thyroiditis. Most patients present with mild thyrotoxic symptoms; lid retraction and lid lag are present, but exophthalmos is absent. The thyroid gland may be diffusely enlarged without tenderness.
- Thyroid storm is a life-threatening medical emergency characterized by decompensated thyrotoxicosis, high fever (often >39.4°C [103°F]), tachycardia, tachypnea, dehydration, delirium, coma, nausea, vomiting, and diarrhea. Precipitating factors include infection, trauma, surgery, radioactive iodine (RAI) treatment, and withdrawal from antithyroid drugs.

## DIAGNOSIS

- Elevated 24-hour radioactive iodine uptake (RAIU) indicates true hyperthyroidism: the patient's thyroid gland is overproducing $T_4$, $T_3$, or both (normal RAIU 10%–30%). A low RAIU indicates that excess thyroid hormone is not a consequence of thyroid gland hyperfunction but is likely caused by thyroiditis, struma ovarii, follicular cancer, or exogenous thyroid hormone ingestion.
- In thyrotoxic Graves' disease, there is an increase in the overall hormone production rate with a disproportionate increase in $T_3$ relative to $T_4$ (**Table 20-1**). Saturation of TBG is increased due to elevated serum levels of $T_4$ and $T_3$, which is reflected in elevated $T_3$ resin uptake. As a result, concentrations of free $T_4$, free $T_3$, and the free $T_4$ and $T_3$ indices are increased to an even greater extent than the measured serum total $T_4$ and $T_3$ concentrations. The TSH level is undetectable due to negative feedback by elevated levels of thyroid hormone at the pituitary. In patients with

symptomatic disease, measurement of serum free $T_4$, total $T_4$, total $T_3$, and TSH will confirm the diagnosis of thyrotoxicosis. If the patient is not pregnant or lactating, an increased 24-hour RAIU indicates that the thyroid gland is inappropriately using iodine to produce more thyroid hormone when the patient is thyrotoxic.

- For toxic adenomas, because there may be isolated elevation of serum $T_3$ with autonomously functioning nodules, a $T_3$ level must be measured to rule out $T_3$ toxicosis if the $T_4$ level is normal. If autonomous function is suspected but the TSH is normal, the diagnosis can be confirmed by failure of the autonomous nodule to decrease iodine uptake during exogenous $T_3$ administration sufficient to suppress TSH.
- In multinodular goiters, a thyroid scan shows patchy areas of autonomously functioning thyroid tissue.
- TSH-induced hyperthyroidism is diagnosed by evidence of peripheral hypermetabolism, diffuse thyroid gland enlargement, elevated free thyroid hormone levels, and elevated serum immunoreactive TSH concentrations. Because the pituitary gland is extremely sensitive to even minimal elevations of free $T_4$, a "normal" or elevated TSH level in any thyrotoxic patient indicates inappropriate production of TSH.
- TSH-secreting pituitary adenomas are diagnosed by demonstrating lack of TSH response to TRH stimulation, inappropriate TSH levels, elevated TSH α-subunit levels, and radiologic imaging.
- In subacute thyroiditis, thyroid function tests typically run a triphasic course in this self-limited disease. Initially, serum $T_4$ levels are elevated due to release of preformed thyroid hormone. The 24-hour RAIU during this time is <2% because of thyroid inflammation and TSH suppression by the elevated $T_4$ level. As the disease progresses, intrathyroidal hormone stores are depleted, and the patient may become mildly hypothyroid with appropriately elevated TSH level. During the recovery phase, thyroid hormone stores are replenished, and serum TSH elevation gradually returns to normal.
- During the thyrotoxic phase of painless thyroiditis, the 24-hour RAIU is suppressed to <2%. Antithyroglobulin and antithyroid peroxidase antibody levels are elevated in more than 50% of patients.
- Thyrotoxicosis factitia should be suspected in a thyrotoxic patient without evidence of increased hormone production, thyroidal inflammation, or ectopic thyroid tissue. The RAIU is low because thyroid gland function is suppressed by exogenous thyroid hormone. Measurement of plasma thyroglobulin reveals presence of very low levels.

TABLE 20-1

**Thyroid Function Tests in Different Thyroid Conditions**

| | Total $T_4$ | Free $T_4$ | Total $T_3$ | TSH |
|---|---|---|---|---|
| Normal | 4.5–10.9 mcg/dL | 0.8–2.7 ng/dL | 60–181 ng/dL | 0.5–4.7 milli-international units/L |
| Hyperthyroid | ↑↑ | ↑↑ | ↑↑↑ | ↓↓* |
| Hypothyroid | ↓↓ | ↓↓ | ↓ | ↑↑* |
| Increased TBG | ↑ | Normal | ↑ | Normal |

*Primary thyroid disease.

## TREATMENT

- Goals of Treatment: Eliminate excess thyroid hormone; minimize symptoms and long-term consequences; and provide individualized therapy

based on the type and severity of disease, patient age and gender, existence of nonthyroidal conditions, and response to previous therapy.

## Nonpharmacologic Therapy

- Surgical removal of the thyroid gland should be considered in patients with a large gland (>80 g), severe ophthalmopathy, or lack of remission on antithyroid drug treatment.
- If thyroidectomy is planned, **methimazole** is given until the patient is biochemically euthyroid (usually 6–8 weeks), followed by addition of **iodides** (500 mg/day) for 10–14 days before surgery to decrease vascularity of the gland.
- **Propranolol** has been used for several weeks preoperatively and 7–10 days after surgery to maintain pulse rate <90 beats/min. Combined pretreatment with propranolol and 10–14 days of **potassium iodide** also has been advocated.

## Pharmacologic Therapy

### Thionamides

- **Methimazole** and **propylthiouracil (PTU)** block thyroid hormone synthesis by inhibiting the peroxidase enzyme system of the thyroid, preventing oxidation of trapped iodide and subsequent incorporation into iodotyrosines and ultimately iodothyronine ("organification"); and by inhibiting coupling of MIT and DIT to form $T_4$ and $T_3$. PTU (but not methimazole) also inhibits peripheral conversion of $T_4$ to $T_3$.
- Usual initial doses include methimazole 30–60 mg daily given in two or three divided doses or PTU 300–600 mg daily (usually in three or four divided doses). Evidence exists that both drugs can be given as a single daily dose.
- Improvement in symptoms and laboratory abnormalities should occur within 4–8 weeks, at which time a tapering regimen to maintenance doses can be started. Make dosage changes monthly because the endogenously produced $T_4$ will reach a new steady-state concentration in this interval.

  Typical daily maintenance doses are methimazole 5–30 mg and PTU 50–300 mg. Continue therapy for 12–24 months to induce long-term remission.
- Monitor patients every 6–12 months after remission. If a relapse occurs, alternate therapy with RAI is preferred over a second course of antithyroid drugs, because subsequent courses are less likely to induce remission.
- Minor adverse reactions include pruritic maculopapular rashes, arthralgias, fever, and benign transient leukopenia (white blood cell count $<4000/mm^3$ or $4 \times 10^9/L$). The alternate thionamide may be tried in these situations, but cross-sensitivity occurs in about 50% of patients.
- Major adverse effects include agranulocytosis (with fever, malaise, gingivitis, oropharyngeal infection, and granulocyte count $<250/mm^3$ or $0.25 \times 10^9/L$), aplastic anemia, lupus-like syndrome, polymyositis, GI intolerance, hepatotoxicity, and hypoprothrombinemia. If agranulocytosis occurs, it usually develops in the first 3 months of therapy; routine WBC count monitoring is not recommended because of its sudden onset.
- Because of the risk of serious hepatotoxicity, PTU should not be considered first-line therapy in either adults or children. Exceptions to this recommendation include (1) the first trimester of pregnancy (when the risk of methimazole-induced embryopathy may exceed that of PTU-induced hepatotoxicity), (2) intolerance to methimazole, and (3) thyroid storm.

### Iodides

- **Iodide** acutely blocks thyroid hormone release, inhibits thyroid hormone biosynthesis by interfering with intrathyroidal iodide use, and decreases size and vascularity of the gland.
- Symptom improvement occurs within 2–7 days of initiating therapy, and serum $T_4$ and $T_3$ concentrations may be reduced for a few weeks.
- Iodides are often used as adjunctive therapy to prepare a patient with Graves' disease for surgery, to acutely inhibit thyroid hormone release and quickly attain the euthyroid state in severely thyrotoxic patients with cardiac decompensation, or to inhibit thyroid hormone release after RAI therapy.

- **Potassium iodide** is available as a saturated solution (**SSKI**, 38 mg iodide per drop) or as **Lugol solution**, containing 6.3 mg of iodide per drop.
- Typical starting dose of SSKI is 3–10 drops daily (120–400 mg) in water or juice. When used to prepare a patient for surgery, it should be administered 7–14 days preoperatively.
- As an adjunct to RAI, SSKI should not be used before but rather 3–7 days after RAI treatment so that the RAI can concentrate in the thyroid.
- Adverse effects of iodide therapy include hypersensitivity reactions (skin rashes, drug fever, and rhinitis, conjunctivitis), salivary gland swelling, "iodism" (metallic taste, burning mouth and throat, sore teeth and gums, symptoms of a head cold, and sometimes stomach upset and diarrhea), and gynecomastia. Iodide is contraindicated in toxic multinodular goiter because the autonomous tissue utilizes the iodine for subsequent thyroid hormone synthesis.

### Adrenergic Blockers

- β-Blockers are used to ameliorate symptoms such as palpitations, anxiety, tremor, and heat intolerance. They have no effect on peripheral thyrotoxicosis and protein metabolism and do not reduce TSAb or prevent thyroid storm. **Propranolol** and **nadolol** partially block conversion of $T_4$ to $T_3$, but this contribution to overall effect is small.
- β-Blockers are usually used as adjunctive therapy with antithyroid drugs, RAI, or iodides when treating Graves' disease or toxic nodules, in preparation for surgery, or in thyroid storm. The only conditions for which β-blockers are primary therapy for thyrotoxicosis are those associated with thyroiditis.
- **Propranolol** doses required to relieve adrenergic symptoms vary, but an initial dose of 20–40 mg orally four times daily is effective for most patients (heart rate <90 beats/min). Younger or more severely toxic patients may require 240–480 mg/day, perhaps because of increased clearance.
- β-Blockers are contraindicated in decompensated heart failure unless it is caused solely by tachycardia (high output). Other contraindications are sinus bradycardia, concomitant therapy with monoamine oxidase inhibitors or tricyclic antidepressants, and patients with spontaneous hypoglycemia. Side effects include nausea, vomiting, anxiety, insomnia, lightheadedness, bradycardia, and hematologic disturbances.
- Centrally acting sympatholytics (eg, **clonidine**) and calcium channel antagonists (eg, **diltiazem**) may be useful for symptom control when contraindications to β-blockade exist.

### Radioactive Iodine

- **Sodium iodide–131** is an oral liquid that concentrates in the thyroid and initially disrupts hormone synthesis by incorporating into thyroid hormones and thyroglobulin. Over a period of weeks, follicles that have taken up RAI and surrounding follicles develop evidence of cellular necrosis and fibrosis of interstitial tissue.
- RAI is the agent of choice for Graves' disease, toxic autonomous nodules, and toxic multinodular goiters. Pregnancy is an absolute contraindication to use of RAI because radiation would be delivered to the fetal tissue.
- β-Blockers are the primary adjunctive therapy to RAI because they may be given anytime without compromising RAI therapy.
- If iodides are administered, they should be given 3–7 days after RAI to prevent interference with uptake of RAI in the thyroid gland.
- Patients with cardiac disease and elderly patients are often treated with thionamides prior to RAI ablation because thyroid hormone levels transiently increase after RAI treatment due to release of preformed thyroid hormone.
- Administering antithyroid drug therapy immediately after RAI may result in a higher rate of posttreatment recurrence or persistent hyperthyroidism.
- Use of lithium as adjunctive therapy to RAI has benefits of increased cure rate, shortened time to cure, and prevention of posttherapy increases in

thyroid hormone levels.

- The goal of therapy is to destroy overactive thyroid cells, and a single dose of 4000–8000 rad results in a euthyroid state in 60% of patients at 6 months or sooner. A second dose of RAI should be given 6 months after the first RAI treatment if the patient remains hyperthyroid.
- Hypothyroidism commonly occurs months to years after RAI. The acute, short-term side effects include mild thyroidal tenderness and dysphagia. Long-term follow-up has not revealed an increased risk for development of mutations or congenital defects.

## Treatment of Thyroid Storm

- Initiate the following therapeutic measures promptly: (1) suppression of thyroid hormone formation and secretion, (2) antiadrenergic therapy, (3) administration of corticosteroids, and (4) treatment of associated complications or coexisting factors that may have precipitated the storm (**Table 20-2**).
- **PTU** in large doses may be the preferred thionamide because it blocks peripheral conversion of $T_4$ to $T_3$ in addition to interfering with thyroid hormone production. However, β-blockers and corticosteroids serve the same purpose. **Methimazole** has a longer duration of action, which offers a theoretical advantage.
- **Iodides**, which rapidly block the release of preformed thyroid hormone, should be administered after a thionamide is initiated to inhibit iodide utilization by the overactive gland.
- Antiadrenergic therapy with the short-acting agent **esmolol** is preferred because it can be used in patients with pulmonary disease or at risk for cardiac failure and because its effects can be rapidly reversed.
- **Corticosteroids** are generally recommended, but there is no convincing evidence of adrenocortical insufficiency in thyroid storm; their benefits may be attributed to their antipyretic action and stabilization of blood pressure (BP).
- General supportive measures, including **acetaminophen** as an antipyretic (avoid aspirin or other nonsteroidal anti-inflammatory drugs, which may displace bound thyroid hormone), **fluid and electrolyte replacement, sedatives, digoxin, antiarrhythmics, insulin**, and **antibiotics** should be given as indicated.

TABLE 20-2

**Drug Dosages Used in the Management of Thyroid Storm**

| Drug | Regimen |
|---|---|
| Propylthiouracil | 900–1200 mg/day orally in four or six divided doses |
| Methimazole | 90–120 mg/day orally in four or six divided doses |
| Sodium iodide | Up to 2 g/day IV in single or divided doses |
| Lugol solution | 5–10 drops three times a day in water or juice |
| Saturated solution of potassium iodide | 1–2 drops three times a day in water or juice |
| Propranolol | 40–80 mg every 6 hours |
| Dexamethasone | 5–20 mg/day orally or IV in divided doses |
| Prednisone | 25–100 mg/day orally in divided doses |
| Methylprednisolone | 20–80 mg/day IV in divided doses |
| Hydrocortisone | 100–400 mg/day IV in divided doses |

## EVALUATION OF THERAPEUTIC OUTCOMES

- After therapy (surgery, thionamides, or RAI) for hyperthyroidism has been initiated, evaluate patients monthly until they reach a euthyroid condition.
- Assess for clinical signs of continuing thyrotoxicosis or development of hypothyroidism.
- If $T_4$ replacement is initiated, the goal is to maintain both the free $T_4$ level and the TSH concentration in the normal range. Once a stable dose of $T_4$ is identified, monitor the patient every 6–12 months.

## HYPOTHYROIDISM: PATHOPHYSIOLOGY

- The vast majority of patients have primary hypothyroidism due to thyroid gland failure caused by chronic autoimmune thyroiditis (Hashimoto disease). Defects in suppressor T lymphocyte function lead to survival of a randomly mutating clone of helper T lymphocytes directed against antigens on the thyroid membrane. The resulting interaction stimulates B lymphocytes to produce thyroid antibodies.
- Iatrogenic hypothyroidism follows exposure to destructive amounts of radiation, after total thyroidectomy, or with excessive thionamide doses used to treat hyperthyroidism. Other causes of primary hypothyroidism include iodine deficiency, enzymatic defects within the thyroid, thyroid hypoplasia, and ingestion of goitrogens.
- Secondary hypothyroidism due to pituitary failure is uncommon. Pituitary insufficiency may be caused by destruction of thyrotrophs by pituitary tumors, surgical therapy, external pituitary radiation, postpartum pituitary necrosis (Sheehan syndrome), trauma, and infiltrative processes of the pituitary (eg, metastatic tumors, tuberculosis).

## CLINICAL PRESENTATION

- Symptoms of hypothyroidism include dry skin, cold intolerance, weight gain, constipation, weakness, lethargy, depression, fatigue, exercise intolerance, loss of ambition or energy, muscle cramps, myalgia, and stiffness. Menorrhagia and infertility are common in women. In children, thyroid hormone deficiency may manifest as growth or intellectual retardation.
- Physical signs include coarse skin and hair, cold or dry skin, periorbital puffiness, bradycardia, and slowed or hoarse speech. Objective weakness (with proximal muscles affected more than distal muscles) and slow relaxation of deep tendon reflexes are common. Reversible neurologic syndromes such as carpal tunnel syndrome, polyneuropathy, and cerebellar dysfunction may also occur.
- Most patients with secondary hypothyroidism due to inadequate TSH production have clinical signs of generalized pituitary insufficiency, such as abnormal menses and decreased libido, or evidence of a pituitary adenoma, such as visual field defects, galactorrhea, or acromegaloid features.
- Myxedema coma is a rare consequence of decompensated hypothyroidism manifested by hypothermia, advanced stages of hypothyroid symptoms, and altered sensorium ranging from delirium to coma. Mortality rates of 60%–70% necessitate immediate and aggressive therapy.

## DIAGNOSIS

- A rise in TSH level is the first evidence of primary hypothyroidism. Many patients have a free $T_4$ level within the normal range (compensated or subclinical hypothyroidism) and few, if any, symptoms of hypothyroidism. As the disease progresses, the free $T_4$ drops below normal. The $T_3$ concentration is often maintained in the normal range despite low $T_4$. Eventually, free and/or total $T_4$ and $T_3$ serum concentrations should be low.
- In secondary hypothyroidism in patients with pituitary disease, serum TSH concentrations are generally low or normal. A serum TSH in the normal range is inappropriate if the patient's $T_4$ is low.

### Treatment of Hypothyroidism (Table 20-3)

- Goals of Treatment: Restore thyroid hormone concentrations in tissue, provide symptomatic relief, prevent neurologic deficits in newborns and children, and reverse the biochemical abnormalities of hypothyroidism.
- **Levothyroxine** (L-thyroxine, $T_4$) is the drug of choice for thyroid hormone replacement and suppressive therapy because it is chemically stable, relatively inexpensive, active when given orally, free of antigenicity, and has uniform potency. Because $T_3$ (and not $T_4$) is the biologically active form, levothyroxine administration results in a pool of thyroid hormone that is readily and consistently converted to $T_3$.
- In patients with longstanding disease and older individuals without known cardiac disease, start therapy with levothyroxine 50 mcg daily and increase after 1 month.
- The recommended initial dose for older patients with known cardiac disease is 25 mcg/day titrated upward in increments of 25 mcg at monthly intervals to prevent stress on the cardiovascular system.
- The average maintenance dose for most adults is ~125 mcg/day, but there is a wide range of replacement doses, necessitating individualized therapy and appropriate TSH monitoring to determine an appropriate dose.
- Although treatment of subclinical hypothyroidism is controversial, patients presenting with marked elevations in TSH (>10 mIU/L) and high titers of thyroid peroxidase antibody or prior treatment with sodium iodide–131 may be most likely to benefit from treatment.
- Levothyroxine is the drug of choice for pregnant women, and the goal is to decrease TSH to the normal reference range for pregnancy.
- Cholestyramine, calcium carbonate, sucralfate, aluminum hydroxide, ferrous sulfate, soybean formula, dietary fiber supplements, and espresso coffee may impair the GI absorption of levothyroxine. Acid suppression with histamine blockers and proton pump inhibitors may also reduce levothyroxine absorption. Drugs that increase nondeiodinative $T_4$ clearance include rifampin, carbamazepine, and possibly phenytoin. Selenium

deficiency and amiodarone may block conversion of $T_4$ to $T_3$.

- **Thyroid USP** (or desiccated thyroid) is usually derived from pig thyroid gland. It may be antigenic in allergic or sensitive patients. Inexpensive generic brands may not be bioequivalent.
- **Liothyronine** (synthetic $T_3$) has uniform potency but has a higher incidence of cardiac adverse effects, higher cost, and difficulty in monitoring with conventional laboratory tests. It must be administered three times a day and may require a prolonged adjustment period to achieve stable euthyroidism.
- **Liotrix** (synthetic $T_4$:$T_3$ in a 4:1 ratio) is chemically stable, pure, and has a predictable potency but is expensive. It also lacks therapeutic rationale because most $T_3$ is converted peripherally from $T_4$.
- Excessive doses of thyroid hormone may lead to heart failure, angina pectoris, and myocardial infarction (MI). Hyperthyroidism leads to reduced bone density and increased risk of fracture.

TABLE 20-3

**Thyroid Preparations Used in the Treatment of Hypothyroidism**

| Drug/Dosage Form | Content | Relative Dose | Comments/Equivalency |
|---|---|---|---|
| Thyroid USP<br>Armour Thyroid, Nature-Throid, and Westhroid ($T_4$:$T_3$ ratio approximately 4.2:1); Armour, 1 grain = 60 mg; Nature-Throid and Westhroid, 1 grain = 65 mg. Doses include 1/4, 1/2, 1, 2, 3, 4, and 5 grain tablets | Desiccated pork thyroid gland | 1 grain (equivalent to 74 mcg [~60–100] mcg of $T_4$) | High $T_3$:$T_4$ ratio; inexpensive |
| Levothyroxine<br>Synthroid, Levothroid, Levoxyl, Levo-T, Unithroid, and other generics 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg tablets; Tirosint 13–150 mcg liquid in gelatin capsule; Tirosint-Sol liquid solution 13, 25, 50, 75, 88, 100, 112, 137, 150, 175, and 200 mcg in unit-dose ampules; 200 and 500 mcg per vial solution for injection | Synthetic $T_4$ | 100 mcg | Stable; predictable potency; generics may be bioequivalent; when switching from natural thyroid to L-thyroxine, lower dose by one half grain; variable absorption between products; half-life = 7 days, so daily dosing; considered to be drug of choice |
| Liothyronine<br>Cytomel 5, 25, and 50 mcg tablets | Synthetic $T_3$ | 33 mcg (~equivalent to 100 mcg $T_4$) | Uniform absorption, rapid onset; half-life = 1.5 days, rapid peak and troughs |
| Liotrix<br>Thyrolar 1/4, 1/2, 1, 2, and 3 grain tablets | Synthetic $T_4$:$T_3$ in 4:1 ratio | Thyrolar 1 = 50 mcg $T_4$ and 12.5 mcg $T_3$ | Stable; predictable; expensive; risk of $T_3$ thyrotoxicosis because of high ratio of $T_3$ relative to $T_4$ |

## Treatment of Myxedema Coma

- Immediate and aggressive therapy with IV bolus **levothyroxine**, 300–500 mcg, has traditionally been used. Initial treatment with IV **liothyronine** or a combination of both hormones has also been advocated because of impaired conversion of $T_4$ to $T_3$.
- Give glucocorticoid therapy with IV **hydrocortisone** 100 mg every 8 hours until coexisting adrenal suppression is ruled out.
- Consciousness, lowered TSH concentrations, and improvement in vital signs are expected within 24 hours.
- Maintenance levothyroxine doses are typically 75–100 mcg IV until the patient stabilizes and oral therapy is begun.
- Provide supportive therapy to maintain adequate ventilation, euglycemia, BP, and body temperature. Diagnose and treat underlying disorders such as sepsis and MI.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Serum TSH concentration is the most sensitive and specific monitoring parameter for adjustment of levothyroxine dose. Concentrations begin to fall within hours and are usually normalized within 2–6 weeks.
- Check both TSH and $T_4$ concentrations every 6 weeks until a euthyroid state is achieved. An elevated TSH level indicates insufficient replacement. Serum $T_4$ concentrations can be useful in detecting noncompliance, malabsorption, or changes in levothyroxine product bioequivalence. TSH may also be used to help identify noncompliance.
- In patients with hypothyroidism caused by hypothalamic or pituitary failure, alleviation of the clinical syndrome and restoration of serum $T_4$ to the normal range are the only criteria available for estimating the appropriate replacement dose of levothyroxine.

*See Chapter 92, Thyroid Disorders, authored by Michael P. Kane and Gary Bakst, for a more detailed discussion of this topic.*