

Iodine Excess and Hyperthyroidism

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150 μg iodine are daily required for thyroid hormone synthesis. The thyroid gland has intrinsic mechanisms that maintain normal thyroid function even in the presence of iodine excess. Large quantities of iodide are present in drugs, antiseptics, contrast media and food preservatives. Iodine induced hyperthyroidism is frequently observed in patients affected by euthyroid iodine deficient goiter when suddenly exposed to excess iodine. Possibly the presence of autonomous thyroid function permits the synthesis and release of excess quantities of thyroid hormones. The presence of thyroid autoimmunity in patients residing in iodine-insufficient areas who develop iodine-induced hyperthyroidism has not been unanimously observed. In iodine-sufficient areas, iodine-induced hyperthyroidism has been reported in euthyroid patients with previous thyroid diseases. Euthyroid patients previously treated with antithyroid drugs for Graves' disease are prone to develop iodine-induced hyperthyroidism. As well, excess iodine in hyperthyroid Graves' disease patients may reduce the effectiveness of the antithyroid drugs. Occasionally iodine-induced hyperthyroidism has been observed in euthyroid patients with a previous episode of post-partum thyroiditis, amiodarone destructive or type II thyrotoxicosis and recombinant interferon- α induced destructive thyrotoxicosis. Amiodarone administration may induce thyrotoxicosis. Two mechanisms are responsible for this condition. One is related to excess iodine released from the drug, approximately 9 mg of iodine following a daily dose of 300 mg amiodarone. This condition is an iodine-induced thyrotoxicosis or type I amiodarone-induced thyrotoxicosis. The other mechanism is due to the amiodarone molecule that induces a destruction of the thyroid follicles with a release of preformed hormones. This condition is called amiodarone-induced destructive thyrotoxicosis or type II thyrotoxicosis. Patients developing type I thyrotoxicosis in general have preexisting nodular goiter whereas those developing type II thyrotoxicosis have a normal thyroid gland. The latter group of patients, after recovering from the destructive process, may develop permanent hypothyroidism as the consequence of fibrosis of the gland.

Introduction

IODINE IS AN ESSENTIAL REQUIREMENT for thyroid hormone synthesis and in the adult the recommended daily iodine intake is 150 μg . In the United States, the median urinary iodine excretion is 14.5 $\mu\text{g}/\text{dL}$. Approximately 5.3% of the population exceeded urinary iodine (UI) of 50 $\mu\text{g}/\text{dL}$ and 1.3% exceeded 100 $\mu\text{g}/\text{dL}$ (1). The thyroid gland has intrinsic regulatory mechanisms that maintain normal thyroid function even in the presence of iodine excess. When large amounts of iodine are given to subjects with normal thyroid function a transient decrease in the synthesis of the thyroid hormones occurs for approx 48 hours. This acute inhibitory effect of iodine on thyroid hormone synthesis is called the acute Wolff-Chaikoff effect and is due to increased intrathyroid iodine concentrations. The escape from or adaption to the acute Wolff-Chaikoff effect is a decrease in the thyroid

iodide trap, thereby decreasing the intrathyroid iodide concentration (2), due to a decrease in the sodium iodide symporter (NIS) mRNA and protein expression (3). Excess iodine ingestion (up to 150 mg/d) also decreases the release of thyroxine (T_4) and triiodothyronine (T_3) from the thyroid resulting in small decreases in serum T_4 and T_3 concentrations with compensatory increases in basal and TRH stimulated thyrotropin (TSH) concentrations, all values remaining well within the normal range (4–9). These iodine-treated subjects remained euthyroid although they continued to ingest the excess iodide and serum thyroid hormone and TSH values returned to basal levels when the iodide was discontinued. These subtle changes in thyroid function were accompanied by increased thyroid volume assessed by echography (8,9) and a decrease in thyroid blood flow determined by color Doppler flow imaging (10). The smallest quantity of iodine, exceeding that consumed with the diet in the United

TABLE 1. COMMONLY USED IODINE-CONTAINING DRUGS

<i>Drugs</i>	<i>Iodine content</i>
Oral or Local	
Amiodarone	75 mg tablet
Benziodarone ^a	49 mg/100-mg tablet
Calcium iodide (e.g., Calcidrine syrup)	26 mg/mL
Diiodohydroxyquin (e.g., Yodoxin)	134 mg/tablet
Echothiophate iodide ophthalmic solution (e.g., Phospholine)	5–41 µg/drop
Hydriodic acid syrup	13–15 mg/mL
Iodochlorhydroxyquin (e.g., Entero-Vioform)	104 mg/tablet
Iodine-containing vitamins	0.15 mg/tablet
Iodinated glycerol (e.g., Organidin, ^b Iophen)	15 mg/tablet 25 mg/mL
Ioxuridine ophthalmic solution (e.g., Herplex)	18 µg/drop
Isopropamide iodide (e.g., Darbid, Combid)	1.8 mg/tablet
Kelp	0.15 mg/tablet
Potassium iodine (KI) (e.g., Quadrinal)	145 mg/tablet 24 mg/mL
Lugol's solution	6.3 mg/drop
Niacinamide hydroiodide + KI (e.g., Iodo-Niacin)	115 mg/tablet
Ponaris nasal emollient	5 mg/0.8 mL
SSKI	38 mg/drop
Parenteral preparations	
Sodium iodide, 10% solution	85 mg/mL
Topical Antiseptics	
Diiodohydroxyquin cream (e.g., Vytone)	6 mg/g
Iodine tincture	40 mg/mL
Iodochlorhydroxyquin cream (e.g., Vioform)	12 mg/g
Iodoform gauze (e.g., NuGauze)	4.8 mg/100 mg gauze
Povidone iodine (e.g., Betadine)	10 mg/mL
Radiology contrast agents	
Diatrizoate meglumine sodium (e.g., Renografin-76)	370 mg/mL
Iodized oil	380 mg/mL
Iopanoic acid (e.g., Telepaque)	333 mg/tablet
Iodate (e.g., Oragrafin)	308 mg/capsule
Iothalamate (e.g., Angio-Conray)	480 mg/mL
Metrizamide (e.g., Amipaque)	483 mg/mL before dilution

^aNot FDA approved.

^bIodine was removed from Organidin and Tuss Organidin in 1995

(Adapted from Braverman LE 1986 Iodide-induced thyroid disease. In: Ingbar SH, Braverman LE (eds) Werner's The Thyroid, 5th ed. Philadelphia, JB Lippincott, p 734.)

States, that does not affect thyroid function is 500 µg/d (11). The administration of 1 mg of iodine per week for 6 weeks followed by the administration of 2 mg of iodine weekly for another 6 weeks did not affect thyroid function (12). Other studies have suggested that the administration of 500 µg iodine daily induced a small but significant increment of basal and TRH stimulated serum TSH concentrations (13,14). Ingestion of 1,500 µg of iodine per day for 15 days by euthyroid subjects invariably resulted in a significant decrease in serum free thyroxine (FT₄) concentrations and FT₄ Index with a significant compensatory rise in basal and TRH stimulated serum TSH concentrations (11,13,14). Pharmacologi-

cal quantities of iodine is almost always due to the administration of inorganic and organic medicinal compounds.

Sources of Excess Iodine

Various drugs and food preservatives contain a large quantity of iodide that is either absorbed directly or released after metabolism of the drug. Many vitamin preparations are supplemented with about 150 µg of iodine, a quantity that is considered to be the physiological daily requirement. Iodophors contain large quantities of iodine and are used as udder antiseptics in the dairy industry, resulting in contam-

TABLE 2. IODINE-INDUCED HYPERTHYROIDISM

Iodine supplementation for endemic iodine-deficiency goiter
Iodine excess administration to patients with euthyroid Graves' disease, especially those in remission after antithyroid drug therapy
Iodine excess administration to euthyroid subjects with previous episode of:
postpartum thyroiditis
amiodarone induced destructive thyrotoxicosis (type II)
IFN- α -induced thyroid dysfunction
Nontoxic nodular goiter
Autonomous nodule
Nontoxic diffuse goiter
Iodine administration to patients with no recognized underlying thyroid disease, especially in area of mild to moderate iodine deficiency

(Adapted from Braverman LE 1986 Iodide-induced thyroid disease. In: Ingbar SH, Braverman LE (eds) Werner's The Thyroid, 5th ed. Philadelphia, JB Lippincott, p 734.)

ination of the milk with iodine. Iodine is also concentrated by the mammary gland and secreted into the milk and, therefore, may influence thyroid function in the newborn who is fed cow's milk. Many iodine-rich products, such as kelp, are available in nature food stores. In some areas of Japan, bread is made exclusively from seaweed, exposing the population to large quantities of iodine.

Iodides are present in high concentration in various proprietary and prescribed expectorants, including iodinated glycerol, Organidin, although iodine has been removed from this latter medication in the United States. Another potential source of excess iodine is the use of contrast media in radiologic studies. Preparations used for computed tomography, arteriography, or pyelography are cleared from the plasma relatively quickly, but the iodine released during these procedures affects thyroid function. However, a dye commonly used for arteriography, meglumine ioxaglate (Hexabrix), did not affect serum T₄, T₃, or FT₄ index up to 56 days after catheterization but serum TSH was not measured (15). Occasionally drinking water may also be a source of excess iodine intake as in some Chinese counties where the drinking water had an iodine concentration of 300 to 462 $\mu\text{g/L}$ resulting in the population residing in those areas to have urinary iodine excretion as high as 900 $\mu\text{g/L}$ (16,17). A partial list of medications and other preparations containing large quantities of iodine is given in Table 1.

Iodide-Induced Hyperthyroidism

Iodide-induced hyperthyroidism is not a single etiologic entity. Since the initial description by Coindet in 1821 (18) and the subsequent definition by Breuer and Kocher in 1904, iodine-induced hyperthyroidism has been reported in patients with a variety of underlying thyroid diseases. As shown in Table 2, iodide-induced hyperthyroidism may occur in patients with iodine-deficiency goiter, in euthyroid Graves' disease patients after antithyroid drug therapy, in euthyroid subjects with previous spontaneous and iatrogenic episodes of thyroid dysfunction, in patients with multinodular goiters who reside in areas of iodine repletion or deficiency, and in people with no evidence of underlying thyroid disease (19-22). The pathogenesis and the epidemiology of iodide-induced hyperthyroidism have been thoroughly reviewed (19,23).

Iodide-Induced Hyperthyroidism in Endemic Iodine-Deficient Areas

Iodine prophylaxis has almost eliminated endemic goiter in many countries. The incidence of iodide-induced hyperthyroidism in areas previously considered iodine deficient varied from no incidence in Austria to 7% in Sweden after iodination programs. The incidence of iodine-induced hyperthyroidism in an endemic goiter area has been estimated to be up to 1.7% (24). The natural course of the disease was mild, and it resolved spontaneously.

Most patients who developed hyperthyroidism have multinodular thyroid disease. Most are euthyroid before iodine administration, but they may have nonsuppressible radioactive iodine uptakes and low or undetectable serum TSH values and the serum TSH may fail to respond to thyrotropin-releasing hormone (TRH). Single oral doses of 200, 400, and 800 mg of iodine administered to adult goitrous subjects residing in the Sudan induced four cases of hyperthyroidism. However, in the three groups of subjects, serum TSH concentrations below 0.1 mU/L were present in 5.9% to 16.7% of the cases 12 months after iodine administration (25). Similar data have been reported 2 years after iodized salt distribution in Zaire. Among 190 adult subjects with nodular goiter, 14 subjects (7.4%) developed severe thyrotoxicosis (26). Thyroid-stimulating antibodies were absent in all. Surprisingly these alterations lasted longer than 1 year (27). Also in Zimbabwe, after the iodination of salt at a level of 30 to 90 ppm, a threefold increase of iodide-induced hyperthyroidism was observed (28). Furthermore, in that population, fatal outcomes occurred mainly from cardiac complications. Delange et al. (29) have suggested that iodine-induced hyperthyroidism occurs only when iodine deficient populations are exposed to a recent (<2 years) excessive increment of alimentary iodine intake.

It appears, therefore, that masked thyroid autonomy becomes evident when iodine repletion permits the autonomous tissue to synthesize and release excess quantities of thyroid hormone. This is consistent with studies from Belgium and Greece (30,31) where the administration of small quantities of iodide (0.5 mg/d) to patients with autonomous nodules induced frank hyperthyroidism. In Austria in 1990, salt iodination was doubled to 20 mg potassium iodide per kilogram salt because before that time the urinary iodine

excretion ranged from 42 to 72 μg of iodine per gram of creatinine (32). This change was accompanied by an increase of the incidence of overt Plummer's disease from 30.5 to 41.7 cases per 100,000 in 1992. The importance of thyroid autonomy for the development of iodide-induced hyperthyroidism is strengthened by a report of iodide-induced hyperthyroidism in a woman with a multinodular goiter treated with suppressive doses of T_4 and simultaneously exposed to high quantities of iodide (33). Attempts have been made to associate iodide-induced hyperthyroidism to thyroid autoimmunity, but the results are conflicting. Long-acting thyroid stimulator (LATS) or LATS protector was found in some patients but not in others (24). In another study, no change in the incidence of thyroid autoantibodies was found after oral administration of iodized oil (34). The oral administration of 0.2 and 0.5 mg of iodine to patients with small, diffuse goiter and low urinary iodine excretion induced the occurrence of subclinical transient hyperthyroidism in the 5% of patients (35,36). These patients had at baseline positive antithyroglobulin (TgAb) and antimicrosomal antibodies (mAb) and titers increased during iodine administration and decreased after withdrawal. A marked increment of overt Graves' disease from 10.4 to 20.9 cases per 100,000 in 1993 was observed in Austria after the increment of salt iodination (32). In contrast to these observation suggesting that iodine-induced hyperthyroidism may be triggered by the development of thyroid autoimmunity, it has been observed that in goitrous schoolchildren, salt iodine supplementation was accompanied by a marked increment of the prevalence of Tg Ab and less commonly thyroperoxidase antibodies (TPOAb) but not by the occurrence of iodide-induced hyperthyroidism (37).

Iodine-Induced Hyperthyroidism in Iodine-Sufficient Areas

In nonendemic euthyroid goiter areas, the incidence of iodine-induced hyperthyroidism is low. Goiter prevalence in the United States is approximately 3.1%, and it is surprising that only a few cases have been reported since the initial re-

port from Boston, Massachusetts, (38), where four of eight patients with goiter developed severe iodine-induced hyperthyroidism after administration of 180 mg of iodide daily for several weeks. Iodine-induced hyperthyroidism has also been reported in other patients residing in the United States (21,39). It is likely that the susceptible patients had nonsuppressible thyroids.

Iodine-induced hyperthyroidism was identified in 13 of 60 hospitalized thyrotoxic elderly subjects in Australia (40,41) and in Germany (42), after nonionic contrast radiography. These subjects did not have positive TPOAb and a thyroid scan revealed the presence of a multinodular goiter. In a prospective study conducted in elderly subjects, it was observed that frank hyperthyroidism was uncommon after the administration of nonionic agents, whereas subclinical hyperthyroidism was observed (43). To reduce the incidence of iodide-induced hyperthyroidism, it has been suggested that methimazole or perchlorate be given the day before and for 2 weeks after x-ray contrast administration to patients with thyroid autonomy (44). Other authors have reported that in euthyroid, not at-risk subjects, iodine-induced hyperthyroidism after coronary angiography was rare and therefore prophylactic therapy was not recommended (45). Lawrence et al. (46) suggested that the administration of thionamide and perchlorate to elderly patients with a suppressed serum TSH and/or palpable goiter might be efficacious. Iodide-induced thyrotoxicosis has also been described in three travelers (travelers' thyrotoxicosis) after the ingestion of iodinated preparations for water purification (47,48). In all three cases, TPOAb were present at the time of the diagnosis of thyrotoxicosis. Iodide-induced thyrotoxicosis occurred in 1 of 40 patients with simple, noniodine-deficient goiter and negative antithyroid antibodies who received 1 mL of iodized oil intramuscularly (49). In these patients, an increment of antithyroid antibodies titer was observed. The large difference in the rate of occurrence of iodide-induced hyperthyroidism between iodine-deficient and iodine-replete areas is difficult to explain. It is possible that people with increased iodine intake are resistant to iodine-induced hyperthyroidism because the sensitivity of the autoregulatory

TABLE 3. FEATURES OF AMIODARONE-INDUCED THYROTOXICOSIS

	<i>Iodine-induced thyrotoxicosis (type I)</i>	<i>Destructive thyrotoxicosis (type II)</i>
Underlying thyroid abnormality	Yes	No
Thyroidal RAIU	Low, normal or elevated	Low
Serum IL-6 concentrations	Slightly elevated	Markedly elevated
Cytologic findings	?	Abundant colloid, hystiocytes vacuolated cells
Pathogenic mechanism	Excessive thyroid hormone synthesis	Excessive thyroid hormone release (destructive thyroiditis)
Response to thionamides	Poor	No
Response to perchlorate	Yes	No
Response to glucocorticoids	?	Yes
Subsequent hypothyroidism	Unlikely	Possible
Effect of excess iodine administration following the thyrotoxic phase	Likely iodine-reinduced hyperthyroidism	Possible iodine-induced hypothyroidism

Modified from Bartalena et al. (62)

RAIU, radioactive iodine uptake; IL-6, interleukin-6.

mechanism has changed, rendering the thyroid better able to handle the excessive quantities of iodide.

Unusual episodes of iodine-induced hyperthyroidism have been observed in a few patients suffering from severe burns treated with povidone iodine (50) and in a patient who had metastatic thyroid carcinoma (51).

Latent Graves' Disease

Antithyroid drug therapy for Graves' disease reduces thyroidal iodine content. Overt hyperthyroidism can develop only if sufficient iodine is available. It has been reported that a small increase in dietary iodine increases the frequency of recurrence of hyperthyroidism after antithyroid drug therapy. The difference in Graves' remission rates between the United States and Europe is attributed, at least in part, to the higher iodine intake in the United States (52). Furthermore, the response to thionamide drugs is rapid in Graves' disease patient who reside in iodine-deficient areas and the dose required to control the disease is smaller (53). It is evident, therefore, that large quantities of iodides administered to patients with latent Graves' disease may result in frank hyperthyroidism.

Consonant with this view are the observations in Graves' disease patients treated with antithyroid drugs. In one study (54) simultaneous administration of methimazole and ipodate reduced the effectiveness of the antithyroid drug. In another study, iodide administration to patients rendered euthyroid after antithyroid drug therapy was accompanied by frank hyperthyroidism in some and with an absent TSH response to TRH in others (55). Excess iodide administered to hyperthyroid patients with Graves' disease significantly increased thyrotropin receptor antibody, suggesting that this phenomenon was responsible for iodine-induced thyroid dysfunction in predisposed subjects (56).

Patients with Previous Thyroid Diseases

Iodide-induced subclinical hyperthyroidism has been observed in 1 of 11 euthyroid women with a previous episode of postpartum thyroiditis receiving 10 drops of saturated solution of KI (SSKI) for 90 days (57).

Iodide-induced subclinical, transient hyperthyroidism occurred also in 20% of euthyroid patients who previously had amiodarone-induced destructive or type II thyrotoxicosis (58). These patients had absent TPOAb and thyrotropin receptor antibodies (TSRAB). Also, euthyroid patients with a previous episode of recombinant interferon- α -induced destructive thyrotoxicosis developed iodide-induced hyperthyroidism in 25% of cases after the administration of pharmacological quantities of iodine (59). These patients did not have circulating TPOAb and TSRAB.

Amiodarone-Induced Thyroid Disease

Amiodarone, a benzofuranic derivative containing 75 mg of iodine per 200-mg tablet, is widely used for the long-term treatment of cardiac arrhythmias. Approximately 9 mg of iodine is released daily during the metabolism of the drug (300-mg dose, which is prolonged with a half-life of approximately 100 days). Amiodarone-induced hyperthyroidism occurs in about 10% of patients residing in iodine-deficient areas (60,61). In the United States, amiodarone-induced hy-

perthyroidism is far less common. These differences are attributed to increased ambient iodine intake in the United States preceding the administration of the drug (60,62).

Amiodarone-induced thyrotoxicosis results from two different mechanisms. The iodine released during the metabolism of the drug is responsible for the thyrotoxicosis in most cases. Predisposing factors include micronodular and macronodular goiter, which are common in older patients who most often require amiodarone. Thyroid autoimmunity has also been incriminated as a predisposing factor and antithyroid antibodies have been found following amiodarone administration in some patients (63) but not in others (64). Amiodarone may also induce destructive thyroiditis resulting in thyrotoxicosis as suggested by clinical, histologic, and *in vitro* studies (64–66). The ultrastructural changes of rat thyroid gland induced by amiodarone are different from those induced by excess iodine and are mediated by a disruption of subcellular organelle function with a marked dilation of the endoplasmic reticulum (67,68). The clinical and laboratory characteristics of amiodarone-induced thyrotoxicosis are presented in Table 3.

The evaluation of thyroid function is difficult in patients receiving amiodarone therapy. Serum T₄ may be elevated, serum T₃ decreased, due to the blocking effect of the drug on type 5' deiodinase, and TSH normal or slightly elevated or decreased in a euthyroid subject receiving the drug. Hyperthyroidism is the best confirmed by suppressed serum TSH and elevated serum T₃ and free T₃ concentrations as well as by an increase in sex hormone-binding globulin (69). The distinction between iodine-induced hyperthyroidism (type I) and destructive thyrotoxicosis (type II) may be achieved by measurement of serum interleukin-6, which is invariably elevated in the destructive form (70) and by fine-needle biopsy, which shows cytologic findings consistent with thyroiditis (66). The thyroid radioiodine uptake is always low in the destructive form and is often low in iodine-induced thyrotoxicosis but may be normal or rarely elevated in rodent-deficient regions. In the latter, ¹³¹I therapy is an alternative.

Distinction of the two forms is important for determining the most efficacious form of therapy. Amiodarone should almost always be discontinued. Large doses of antithyroid drugs are recommended for iodine-induced hyperthyroidism. If this treatment fails, potassium perchlorate (250 mg three times daily) should be added (71,72). The latter drug blocks the thyroid iodide trap, thereby decreasing the intrathyroidal iodide content.

In patients with destructive thyrotoxicosis, administration of large doses of corticosteroids is rapidly effective (66,73). Normal serum T₃ concentrations were achieved after an average of eight days. Relapses are frequent as the prednisone dose was tapered (74). Surgery has been successfully used for the treatment of amiodarone-induced thyrotoxicosis (75).

After recovering from amiodarone-induced destructive thyrotoxicosis, patients may develop permanent hypothyroidism (66,76) as a result of fibrosis of the gland (77). The iodine-perchlorate discharge test was positive in 60% of euthyroid patients who had recovered from amiodarone-induced destructive thyrotoxicosis (78). The long-term administration of 300 mg of iodide daily to these patients induced a marked increase in basal and TRH-stimulated serum TSH concentrations, which returned to normal after iodide with-

drawal. Finally, adult patients with β -thalassemia have been shown to be particularly prone to develop both hyperthyroidism and hypothyroidism during amiodarone therapy for heart failure or cardiac arrhythmias (79).

In view of the high incidence of thyroid dysfunction, amiodarone should be administered with caution to patients with preexisting goiter or a history of thyroid disease. Before beginning amiodarone treatment, a careful examination is required; TSH and TPOAb values are mandatory. During amiodarone treatment measurement of serum TSH concentrations is required approximately every 6 months in order to detect the development of mild thyroid disorders.

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