Iodine-Induced Hypothyroidism

K. Markou, N. Georgopoulos, V. Kyriazopoulou, and A.G. Vagenakis

Iodine is an essential element for thyroid hormone synthesis. The thyroid gland has the capacity and holds the machinery to handle the iodine efficiently when the availability of iodine becomes scarce, as well as when iodine is available in excessive quantities. The latter situation is handled by the thyroid by acutely inhibiting the organization of iodine, the so-called acute Wolff-Chaikoff effect, by a mechanism not well understood 52 years after the original description. It is proposed that iodopeptide(s) are formed that temporarily inhibit thyroid peroxidase (TPO) mRNA and protein synthesis and, therefore, thyroglobulin iodinations. The Wolff-Chaikoff effect is an effective means of rejecting the large quantities of iodide and therefore preventing the thyroid from synthesizing large quantities of thyroid hormones. The acute Wolff-Chaikoff effect lasts for few days and then, through the so-called “escape” phenomenon, the organization of intrathyroidal iodide resumes and the normal synthesis of thyroxine (T₄) and triiodothyronine (T₃) returns. This is achieved by decreasing the intrathyroidal inorganic iodine concentration by down-regulation of the sodium iodine symporter (NIS) and therefore permits the TPO-H₂O₂ system to resume normal activity. However, in a few apparently normal individuals, in newborns and fetuses, in some patients with chronic systemic diseases, euthyroid patients with autoimmune thyroiditis, and Graves’ disease patients previously treated with radioimmunoassay (RAI), surgery or antithyroid drugs, the escape from the inhibitory effect of large doses of iodides is not achieved and clinical or subclinical hypothyroidism ensues. Iodide-induced hypothyroidism has also been observed in patients with a history of postpartum thyroiditis, in euthyroid patients after a previous episode of subacute thyroiditis, and in patients treated with recombinant interferon-α who developed transient thyroid dysfunction during interferon-α treatment. The hypothyroidism is transient and thyroid function returns to normal in 2 to 3 weeks after iodide withdrawal, but transient T₄ replacement therapy may be required in some patients. The patients who develop transient iodine-induced hypothyroidism must be followed long term thereafter because many will develop permanent primary hypothyroidism.

Introduction

Iodine is an essential element for the formation of the thyroid hormones, triiodothyronine (T₃) and thyroxine (T₄), which play an important role in the development, growth, and metabolism of almost all organ systems. The thyroid gland has the capacity and holds the machinery to maintain the synthesis and secretions of thyroid hormones even when the availability of iodine becomes scarce, or when it is available in excessive amounts. Thus, in iodine deficiency the decrease in iodine availability results in an increase in TSH secretion, thyroid growth is stimulated resulting in a goiter formation, the iodine trapping mechanism is enhanced and there is a shift of the intrathyroidal formation of T₄ to the more active metabolite T₃. On the other hand, an increased iodide load to the normal thyroid can be easily handled by an autoregulatory mechanism independent of thyrotropin (TSH). The purpose of this manuscript is to review the effects of excessive iodine intake on thyroid hormone economy in patients with an apparently normal thyroid gland function and in those prone to develop clinical or subclinical hypothyroidism when exposed to pharmacological doses of iodides.

Physiological Effects of Iodide on Thyroid Function

In 1944 Morton et al. (1) made the seemingly paradoxical observation that the addition of large quantities of iodide to the culture of sheep thyroid slices, inhibited the organic form of iodide. Wolff and Chaikoff (2) later demonstrated that a similar effect could be elicited in vivo by administering large doses of iodide to rats sufficient to maintain high levels of plasma inorganic iodide concentration. This finding was seemingly similar to that induced by the antithyroid drugs such as methimazole and propylthiouracil (PTU). With the passage of time, the intrathyroidal iodide concentration pre-
sumably decreased, the organization of the remaining iodine resumed and returned to pretreatment quantities. The acute inhibition of the formation of organic iodine was then called the acute Wolff-Chaikoff effect and the resumption of the organization of iodine was named the “escape” or “adaptation” phenomenom. The small proportion of organic iodine formed during the acute Wolff-Chaikoff effect was found to be incorporated mainly into monoiodotyrosine (MIT) relative to diiodotyrosine (DIT) leading to an increased MIT/DIT ratio (3). A decreased quantity of iodothyronines were formed, a characteristic effect of antithyroid drugs (4).

It is, therefore, apparent that the acute Wolff-Chaikoff effect operating in a normal thyroid gland is a successful means of preventing the thyroid from forming massive quantities of thyroid hormones, thus preventing a hyper-thyroid state to ensue. The adaptive response of the thyroid to small or moderate increments in the available iodine, however, is not perfect. In 1964, Nagataki and Ingbar (5) studied the acute response to a greater range of iodide doses in the rat. With small or moderate doses administered, total organic iodine was increased and the apportionment of organic iodine to MIT, DIT, T₄, and T₃ was not altered. However, after a critical point (i.e., 250 μg/250 g rat) a sharp decline in the total organified iodine was accompanied by an increase in the MIT/DIT ratio and a decrease in T₄ and T₃ formation.

These findings demonstrated that the proposed autoregulation of intrathyroidal iodine fails to protect the thyroid from smaller quantities of iodine and that hormonal formation indeed increases (5). The mechanism responsible for the acute Wolff-Chaikoff effect remains elusive despite the 52 years since the original observation. The pioneer work of Raven (6) clearly showed

Table 1. Commonly Used Iodine-Containing Drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Iodine content</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral or local</strong></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>75 mg/tablet</td>
</tr>
<tr>
<td>Benziodarone</td>
<td>49 mg/100-mg tablet</td>
</tr>
<tr>
<td>Calcium iodide (e.g., Calcidrine Syrup)</td>
<td>26 mg/ML</td>
</tr>
<tr>
<td>Diiodohydroxyquin (e.g., Yodoxin)</td>
<td>134 mg/tablet</td>
</tr>
<tr>
<td>R-Gen</td>
<td>6 mg/mL</td>
</tr>
<tr>
<td>Echothiophate iodide opthalmic solution</td>
<td>5–41 μg/drop</td>
</tr>
<tr>
<td>Hydriodic acid syrup</td>
<td>13–15 mg/ML</td>
</tr>
<tr>
<td>Iodochlorhydroxyquin (e.g., Entero-Vioform)</td>
<td>104 mg/tablet</td>
</tr>
<tr>
<td>Iodine-containing vitamins</td>
<td>0.15 mg/tablet</td>
</tr>
<tr>
<td>Iodinated glycerol (Iophen)</td>
<td>15 mg/tablet</td>
</tr>
<tr>
<td>Idoxuridine opthalmic solution</td>
<td>18 μg/drop</td>
</tr>
<tr>
<td>Isopropamide iodide (e.g., Darbid.Combid)</td>
<td>1.8 mg/tablet</td>
</tr>
<tr>
<td>Kelp</td>
<td>0.15 mg/tablet</td>
</tr>
<tr>
<td>Potassium iodine (KI) (e.g., Quadrinal, pima syrup)</td>
<td>24 mg/mL, 255 mg/mL</td>
</tr>
<tr>
<td>Mudrane</td>
<td>195 mg/tablet</td>
</tr>
<tr>
<td>Lugol’s Solution</td>
<td>6.3 mg/drop</td>
</tr>
<tr>
<td>Niacinamide hydroiodide + KI (e.g., Iodo-Niacin)</td>
<td>115 mg/tablet</td>
</tr>
<tr>
<td>Ponaris nasal emollient</td>
<td>5 mg/0.8 mL</td>
</tr>
<tr>
<td>SSKI</td>
<td>38 mg/drop</td>
</tr>
<tr>
<td><strong>Parenteral preparations</strong></td>
<td></td>
</tr>
<tr>
<td>Sodium iodide, 10% solution</td>
<td>85 mg/mL</td>
</tr>
<tr>
<td><strong>Topical antiseptics</strong></td>
<td></td>
</tr>
<tr>
<td>Diiodohydroxyquin cream (e.g., Vytone)</td>
<td>6 mg/g</td>
</tr>
<tr>
<td>Iodine tincture</td>
<td>40 mg/mL</td>
</tr>
<tr>
<td>Iodochlorhydroxyquin cream (e.g., Vioform)</td>
<td>12 mg/g</td>
</tr>
<tr>
<td>Cellasene</td>
<td>720 μg/serving</td>
</tr>
<tr>
<td>Iodoform gauze (e.g., NuGauze)</td>
<td>4.8 mg/100 mg gauze</td>
</tr>
<tr>
<td>Povidone iodine (e.g., Betadine)</td>
<td>10 mg/mL</td>
</tr>
<tr>
<td><strong>Radiology contrast agents</strong></td>
<td></td>
</tr>
<tr>
<td>Diatrizoate meglumine sodium (e.g., Renografin-76)</td>
<td>370 mg/mL</td>
</tr>
<tr>
<td>Iodized oil</td>
<td>380 mg/mL</td>
</tr>
<tr>
<td>Iopanoic acid (e.g., Telepaque)</td>
<td>333 mg/tablet</td>
</tr>
<tr>
<td>Ipodate (e.g., Oragrafin)</td>
<td>308 mg/capsule</td>
</tr>
<tr>
<td>Iothalamate (e.g., Angio-Conray)</td>
<td>480 mg/mL</td>
</tr>
<tr>
<td>Metrizamide (e.g., Amipaque)</td>
<td>483 mg/mL before dilution</td>
</tr>
<tr>
<td>Lipiodol™</td>
<td>480 mg/mL</td>
</tr>
</tbody>
</table>

*Not FDA approved

*a Iodine 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.)
that the critical parameter for the Wolff-Chaikoff effect was the amount of intrathyroidal iodine and not the plasma concentration. It was also proposed that the iodine-to-newly-formed thyroglobulin ratio (I:Tg) was critical for iodinations. Iodine-deficient rats treated with small quantities of the protein inhibitor cycloheximide, and given small quantities of iodides (12 µg per rat), permitted induction of the acute Wolff-Chaikoff effect by an intrathyroidal concentration of iodine insufficient to produce this effect in control animals (7).

The above experimental data, however, do not fully explain the acute Wolff-Chaikoff effect. One postulate ascribes the effect to an interaction of oxidized iodine with excess iodide to yield the triiodide ion I$_3^-$, a moiety known to be incapable to carry out organic iodinations (8). Recently, organic iodocompounds formed within the thyroid were proposed as a possible mechanism. α-Iodohexadecanal, a major iodo-lipid has been shown to inhibit nicotinamide adenine, dinucleotide phosphate oxidase, thyroid peroxidase, and TSH-induced cyclic adenosine monophosphate (cAMP) formation in the thyroid (9).

Evidence concerning the mechanism of escape was lacking until the ingenious experiments of Braverman and Ingbar in 1963 (10). Studies on iodine metabolism were carried out in rats and concluded that adaptation to long-term iodide exposure was caused by a decrease in iodine transport, thereby reducing the intrathyroidal iodine concentration below the critical inhibitory levels, therefore, allowing the iodinations to resume (10). It was pointed out that the adaptation was TSH-independent because it occurred in normal and hypophysectomized rats. The recent cloning of the sodium iodide symporter (NIS) by Dai et al. (11) led Braverman’s group to reexamine the role of this protein in the adaptation of long-term exposure to iodides. Both NIS mRNA and protein were decreased at 1 and 6 days after long-term iodide ingestion. Thyroid peroxidase (TPO) mRNA was decreased at 6 days of long-term iodide ingestion and 24 hours after an acute iodide load (12). Similar results were reported in hypothyroid dogs treated for 48 hours with moderate doses of iodides. The expression of NIS and TPO mRNA was inhibited and the half-life of NIS protein was calculated to be 4 days in the dog (13). These data are in agreement with the data published 37 years ago (10) and support the hypothesis that the escape from the acute Wolff-Chaikoff effect is caused by a decrease of NIS protein resulting in a decrease in the thyroidal iodine transport.

**Induction of Hypothyroidism and/or Goiter by Excess Iodide**

Many patients are exposed to large quantities of iodide present in proprietary medications, in food as a preservative, and in x-ray contrast media (Table 1). Despite the widespread use of excess iodide, few apparently normal subjects with normal thyroid function prior to iodide exposure develop thyroid dysfunction. However, in subjects with underlying thyroid disease not readily apparent, exposure to large doses of iodide usually results in hypothyroidism and/or goiter which abates after iodide withdrawal (Table 2). Less frequent, but much more difficult to treat and occasionally life-threatening, thyrotoxicosis may follow iodide exposure as discussed elsewhere (14) and in this issue.

**Table 2. Iodine-Induced Hypothyroidism or Goiter**

<table>
<thead>
<tr>
<th>Normal subjects</th>
<th>With underlying thyroid disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetus and neonate</td>
<td>Hashimoto’s thyroiditis</td>
</tr>
<tr>
<td>Infant</td>
<td>Graves’ disease (after euthyroidism by $^{131}$I, thyroidectomy or drug therapy)</td>
</tr>
<tr>
<td>Adults (high iodine intake in Japan)</td>
<td>Subclinical hypothyroidism, especially in the elderly</td>
</tr>
<tr>
<td>Elderly</td>
<td>after post partum thyroiditis after hemithyroidectomy for benign nodules</td>
</tr>
<tr>
<td>Chronic nonthyroidal illness</td>
<td>after amiodarone destructive thyrotoxicosis</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>post-interferon-α–induced thyroid dysfunction</td>
</tr>
<tr>
<td>Chronic dialysis treatment</td>
<td></td>
</tr>
<tr>
<td>Thalassemia major</td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy (?)</td>
<td></td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td></td>
</tr>
</tbody>
</table>

**Synergism with other drugs**

- Lithium, sulfisoxazole, sulfadiazine (?)

Adapted from Roti and Vagenakis (14).

**Normal subjects**

Iodide-induced goiter occurred in about 10% in the coastal regions of Hokkaido, a northern island of Japan (15,16). The inhabitants of this region were consuming large quantities of seaweed, especially kelp (Laminaria) containing large quantities of iodide. It has been estimated that the quantity of iodide ingested daily may exceed 200 mg. Such goiter has now disappeared after the restriction of intake of kelp products in the affected areas (17,18). However, Kono et al. (19) reported that in coastal areas of the Hokkaido Islands, the prevalence of nonautoimmune hypothyroidism was still 9.7% in some areas and it was proportional to iodide intake whereas the incidence of nonautoimmune thyrotoxicosis was not related to iodide consumption. In an earlier study, Kono et al. (20) reported that when the iodine intake was restricted, the increased serum TSH concentrations was normalized in patients with negative antithyroid antibodies but remained elevated in those with positive antibodies. This suggests that iodine-induced hypothyroidism was an additional component to the etiology of hypothyroidism due to autoimmune thyroiditis.

Similar results were reported by Szabolcs et al. (21) in Slovakia where the cumulative prevalence of hypothyroidism increased progressively in relation to urinary iodine excretion of 72, 100, and 513 µg/g creatinine. Endemic iodide goiter has also been observed in 64% of children in an area located in central China consuming water containing approximately 500 µg/L (22). In another study from China, euthyroid goiter was observed in 10% of the subjects of 19 Chinese counties caused by iodine-rich drinking water (23).

Ingestion of smaller quantities of iodine may affect thyroid function in a population at large. In an elderly Icelandic population, the prevalence of serum TSH concentrations above 4 mIU/L was 18% in subjects with elevated iodine excretion rates (33 to 703 µg/L; median, 150 µg/L) whereas in
subjects residing in Jutland with low urinary iodine secretion (median, 38 μg/L; range, 6–770), low TSH levels (<0.4 mU/L) were the prevalent finding in 9.7% of the cases. There were no differences in the prevalence of antithyroid antibodies in the two populations (24).

Despite the evidence provided by the previous studies it is still controversial whether completely normal subjects may develop perturbed thyroid function when these subjects are exposed to large doses of iodide. We did not observe abnormal thyroid function tests in 20 normal adults treated with 80 mg of Lugol’s solution for 2 months (25). Administration of a single dose of 50 to 70 mg of potassium iodide to children for prophylaxis after the Chernobyl reactor accident was not accompanied by an increment in the serum TSH concentration (26). We believe that iodine-induced hypothyroidism does occasionally occur in normal individuals but is exceedingly rare.

Histologic examination of the thyroid of patients with iodine-induced hypothyroidism revealed extensive lymphocytic infiltration in half of the examined thyroids. Various other findings were observed in other specimens including hyperplasia in the follicles with papillary foldings, columnar, or cuboidal changes in cells with clear and vesicular cytoplasm and markedly reduced colloid. Most of these findings reversed after iodine withdrawal (27).

Iodide Goiter and Hypothyroidism in the Newborn

Iodide is readily transferred across the placenta. This may be by active transport in rats but there are no data in humans (28). Iodide may lead to goiter in the newborn in mothers treated for chronic lung disease. The true incidence of hypothyroidism in the newborn infants has not been accurately assessed, although many of them have suggestive evidence of hypothyroidism. Six of 25 and 8 of 22 newborn infants with iodide goiter died of tracheal obstruction and asphyxiation (reviewed by Wolff [28], Benhard et al. [29], and Nagle et al. [30]). Although iodide goiter of the newborn usually disappears in a few months, surgical intervention is often indicated to relieve tracheal obstruction (31,32). Diagnosis and treatment of fetal goiter and hypothyroidism can be obtained by ultrasonography and cordocentesis, as judged by the diagnosis of fetal goiter in a fetus whose asthmatic mother consumed two to three spoonfuls daily of a syrup containing 150 mg per 15 mL of iodide (33).

NIS expression has been found in lactating mammary glands and iodine is actively transported by the breast tissue and is secreted into the milk. Studies in the rat revealed that iodide goiter and hypothyroidism was sustained in nursing pups up to 20 days of nursing dams ingesting large doses of iodides (34).

The thyroid of the fetus and newborn can be exposed to large doses of iodide from various sources. In nonpregnant women, vaginal use of povidone-iodine pessaries do not affect thyroid function. However, application of vaginal solutions or cream of povidone iodide resulted in transient hypothyroidism in the newborn especially when the iodide use was continued during the third trimester of pregnancy and during labor (35,36). Topical application of povidone iodine and administration of an iodinated contrast dye to the newborn resulted in an elevation of serum TSH especially in premature low birthweight infants. This was observed mainly in Europe where iodine intake is relatively low (37–40). Transient hypothyroidism was not a common sequela of routine skin cleansing with iodine in premature newborn infants in North America (41).

After the Chernobyl nuclear reactor accident a single dose of 15 mg of potassium iodide was administered to newborns for radiation prophylaxis of the thyroid. A transient increase of serum TSH concentration was observed in 0.37% of the 3,214 treated newborns. Similarly, exposure of the thyroid to iodine in utero due to maternal iodide prophylaxis did not result in an increase in congenital hypothyroidism as judged by screening studies (26). However, it must be pointed out that, at least in Europe, iodide consumption is the major cause of transient congenital hypothyroidism, resulting in 3% of recalls of newborns for verification of hypothyroidism in comparison with 0.1% in newborns from mothers with normal iodine intake (37–40). As mentioned above, this is attributed to relatively low iodine intake in Central Europe in contrast to North America where iodine intake is adequate (41). A number of infants born of mothers suffering from thyrotoxicosis and treated with iodides or Lugol’s solution have been reported to have goiter (28). Approximately 6% of newborns from mothers with Graves’ disease living in Japan who treated with 6 to 40 mg iodine daily from 11 to 37 weeks of gestation had elevated cord blood serum TSH concentrations but normal concentration of thyroid hormones (42). It must be noted, however, that the lack of fetal-iodine-induced hypothyroidism in those newborns may be caused by the concomitant presence of autoimmune thyroid hyperfunction and the high ambient iodine intake in Japan.

Iodine-containing drugs consumed during pregnancy by the mother may also result in iodine-induced hypothyroidism in the fetus. A few cases of amiodarone-induced hypothyroidism in the newborn were reported from North America (43) and Europe (44).

Iodine-Induced Hypothyroidism in Nonthyroidal Illness

Patients with chronic nonthyroidal illness are not susceptible to the inhibitory effects of iodide. A few cases, however, have been reported to occur in such patients but an accompanying underlying disease has not been excluded in these cases. Iodides administered to patients with chronic obstructive pulmonary diseases including asthma may lead to hypothyroidism in some cases. However, underlying Hashimoto’s thyroiditis which predispose these patients to the inhibitory effects of iodine was not ruled out (14).

Children with cystic fibrosis treated with sulfisoxazole have been reported to be susceptible to iodine-induced hypothyroidism. No apparent underlying thyroid abnormality has been found in these patients (45). Increased amount of lipofuscin has been reported in patients with cystic fibrosis but this has also been found in mice fed large quantities of iodides.

The effect of long-term iodide administration to normal children has not been evaluated. Markou et al administered 80 mg potassium iodide to 30 normal children 8 to 14 years old for 3 months and none developed overt or subclinical hypothyroidism. Transient elevated serum TSH values (5–8 mU/L) were noted in 70% of the children, usually during the first 2 to 3 weeks after the beginning of iodide administration. TSH returned to normal levels despite the continuation of iodide treatment (46).
In children and adults suffering from thalassemia major and who require long-term blood transfusion therapy, iodide administration (60 mg daily) for 30 days resulted in subclinical hypothyroidism in 70% of pubertal and 47% of adult patients. In all patients, TSH levels returned to pretreatment levels after iodide withdrawal. In the follow-up of these patients for 5 years, 64% of those who developed transient hypothyroidism during iodide administration developed permanent clinical hypothyroidism. Only 1 of the 11 patients who remained normal during iodide administration became hypothyroid during the 5 years of observation. It appears that thyroid hemosiderosis renders the thyroids of these patients susceptible to the inhibitory effects of iodide (47).

Patients with chronic renal failure may develop thyroid dysfunction when exposed to large doses of iodide. Iodine is cleared mainly by the kidney, and in renal failure the plasma inorganic iodine has been found to increase substantially. The incidence of iodine-induced hypothyroidism was found in 3.2% of patients on chronic dialysis treatment (48). The thyroid abnormalities in these patients included, thyroid enlargement, normal or elevated thyroid RAI uptakes, positive perchlorate discharge tests, and absence of lymphocyte infiltration. Two patients with diabetic nephropathy developed iodine-induced nonautoimmune hypothyroidism that was reversed after iodide restriction in one patient and hemodialysis treatment in the other (49). However, in another study, no relationship was found to exist between thyroid abnormalities to iodide retention and application of iodide-containing antiseptics (50).

Iodine-induced hypothyroidism was also reported in patients with no apparent thyroid disease. Mild reversible hypothyroidism was observed in elderly patients consuming iodinated glycerol (51). One patient developed hypothyroidism after treatment with eye drops of eechothiophate iodide (52). Two Japanese patients with anorexia nervosa developed iodine-induced hypothyroidism. One patient became hypothyroid during the bulimic period of the disease due to consumption of large quantities of Oshaberi-Kombu. In Japan, this food is extensively consumed as low-calorie food and one package of Oshaberi-Kombu contains approximately 13.4 mg of iodine (14, 53).

Patients with Underlying Thyroid Disease

Patients with underlying, perhaps mild, autoimmune thyroid disease such as Hashimoto's thyroiditis are particularly susceptible to developing iodine-induced hypothyroidism over the ensuing several weeks after the exposure. Most patients with Hashimoto's thyroiditis exhibit a positive iodine-perchlorate discharge test suggesting a defect in the intrathyroid organic binding of iodine. The first study that conclusively demonstrated the susceptibility of these patients to iodine induced hypothyroidism was done in 1972 when 50% of patients with histologically proven autoimmune thyroiditis developed frank hypothyroidism after administration of 180 mg of iodide daily. The hypothyroidism was observed 2 to 8 weeks after the initiation of iodide administration and was reversed between 2 to 4 weeks after iodide withdrawal. The iodine-perchlorate discharge test was positive in those who developed iodine hypothyroidism and negative in those who did not (54).

Contradictory results have been obtained when susceptible patients with Hashimoto's thyroiditis are exposed to a moderately increased iodine intake. In one study, ingestion of 1.5 mg of iodide daily for 3 months did not affect thyroid function in such patients (55). In a few Japanese patients with elevated alimentary iodide intake and hypothyroidism, restriction of iodide intake restored normal thyroid function. All had an underlying lymphocytic thyroiditis (56). It must be noted that a large number of these patients developed permanent hypothyroidism with the passage of time even in the presence of normal serum plasma inorganic iodine, suggesting that patients susceptible to transient iodine-induced hypothyroidism are at high risk to develop permanent hypothyroidism, probably due to the underlying destructive autoimmune process in the thyroid.

Small doses of iodide (i.e., 250 μg of iodide per day) were given to 40 patients with positive TPO antibodies and residing in an area of mild iodine deficiency. Eight of them developed subclinical and clinical hypothyroidism and no changes in TPO levels (57). All had TSH higher than 3 mU/L before iodide treatment suggesting incipient thyroid dysfunction. In a recent report from India, patients with juvenile autoimmune thyroiditis develops overt clinical (6.5%) or biochemical hypothyroidism (15%) after salt iodization (58). In another study, a transient increase of serum T4 and T3 concentrations followed the administration of small quantities of iodide in patients with TPO-positive antibodies residing in an area with low ambient iodine intake (59).

Studies in rats that were genetically susceptible to chronic lymphocytic thyroiditis (BB/woo rats) and that were fed large quantities of iodide, surprisingly did not develop an increased incidence of hypothyroidism, and no demonstrable abnormality in intrathyroidal iodine organified was found (60). However, in rats demonstrating the most extensive lymphocytic thyroiditis, iodide administration does induce hypothyroidism (61).

Patients with Graves' disease were treated with iodides alone when the antithyroid drugs were not available. Few of them developed reversible hypothyroidism, and in some, the hyperthyroidism worsened during iodide treatment. Euthyroid patients with Graves' disease treated years earlier with 131I, thyroidectomy or antithyroid drugs, are also inordinately sensitive to iodine-induced hypothyroidism (14). Hypothyroidism was rapidly developed in 100% of patients treated with 131I and in 40% of those treated surgically (62).

It appears that an underlying organification defect is present in all patients with Graves' disease who developed iodine hypothyroidism because a positive iodine perchlorate discharge test was present. Whether this iodine sensitivity is an inherent component of Graves' disease or to a therapy-induced effect is at present not definite.

The etiology of surgically treated patients with Graves' disease to iodine-induced hypothyroidism is not readily apparent. Similar susceptibility to the inhibitory effect of pharmacologic doses of iodide is observed in patients undergoing hemithyroidectomy for a benign thyroid nodule, and in hemithyroidectomized BB/woo rats prone to develop lymphocytic thyroiditis (63, 64). It appears that the hyperfunctioning thyroid remnant is unable to adapt to iodide excess. It is questionable, however, whether the thyroid gland of a patient with a thyroid nodule should be considered normal.

There are several other thyroid diseases that can predispose susceptible individuals to iodine-induced hypothyroidism.
roidism. Women who are euthyroid after a previous episode of postpartum thyroiditis are prone to iodine-induced hypothyroidism. In 9 of 11 women, ingestion of 300 mg of iodide daily resulted in overt reversible hypothyroidism and in some was accompanied by a goiter (65). Most of these patients had a positive perchlorate discharge test. Small doses of iodide administered to patients predisposed to developing postpartum thyroiditis intensified rather than ameliorated the disease (66). In another study, however, smaller quantities of iodine supplementation (150 μg/d) administered during pregnancy and in the postpartum period, to TPO-Ab-positive women living in an area with mild to moderate iodine deficiency did not induce or worsen postpartum thyroid disease (67).

Patients who have recovered from subacute thyroiditis may develop iodide hypothyroidism when exposed to large doses of iodide, long after the remission of the painful febrile episode. In 10 of 18 subjects, ingestion of 300 mg of iodine resulted in a significant but slight increase in serum TSH concentration. Two of these patients had values higher than 50 mU/L accompanied by goiter (68). Weetman et al. (69) have reported that persistent autoimmunity was found up to 39 months after the episode of subacute thyroiditis but the exact nature of their autoimmunity remains unclear, because they were negative for Tg and antimicrosomal antibodies. The reactive antigen was found in the 2,000-g supernatant of crude thyroid extract.

Treatment of chronic active hepatitis with recombinant interferon-α (rINF-α) may result in thyroid dysfunction (70). Transient hypothyroidism is a common complication that usually ameliorates after the interferon therapy is discontinued. Euthyroid patients with interferon-induced thyroid dysfunction are prone to developing iodine-induced hypothyroidism and some may develop hyperthyroidism independent of the presence or absence of thyroid antibodies (71,72). Minelli et al. (73) recently reported that excess iodine administered for 2 months to patients with chronic hepatitis C virus treated with rINF-α induced small changes in thyroid function similar to those observed in patients treated with iodine alone. This suggests that iodides do not have synergistic effects with interferon-α to induce thyroid dysfunction at least for 2 months.

Synergism with Other Drugs

The sulfonamides, sulfadiazines, and sulfisoxazole are mild inhibitors of thyroid hormone synthesis and when administered alone, they do not exert an apparent effect on thyroid function. In patients with cystic fibrosis who were treated with sulfisoxazole, iodide administration resulted in goiter formation in some and subclinical hypothyroidism in others (45).

Lithium has multiple effects on thyroid function, including inhibition of organification of iodine and the release of thyroid hormones. Hypothyroidism has been reported in a few patients treated with lithium when exposed to high iodide intake. Conversely iodine deficiency may act as a protective factor during lithium therapy, as judged by the lack of reports from countries with low iodine intake such as Germany, Italy, and Spain (74).

Amiodarone-Induced Hypothyroidism

Special emphasis must be given to amiodarone, a benzofuranic derivative used for long-term treatment of cardiac arrhythmias. It contains 75 mg of iodine per 200-mg tablet and has a prolonged half-life of at least 100 days. Approximately 9 mg of iodine is released daily during the metabolism of the drug (300 mg dose). Amiodarone-induced hypothyroidism is more common than thyrotoxicosis (75). In the United States it may occur in 20% of patients treated with amiodarone whereas thyrotoxicosis is far less common. The reverse is true in Italy, a country with low ambient iodine intake (75). These differences are attributed to increased ambient iodine intake in the United States.

The mechanism by which amiodarone induces hypothyroidism can be partly explained by the excess of iodine released during the metabolism of the drug. Measurement of intrathyroid iodine content by radiographic fluorescence revealed increased iodine content in patients with hypothyroidism following amiodarone administration (59). Administration of potassium perchlorate, which prevents thyroid iodine uptake and permits the egress of nonorganified intrathyroid iodine, restored euthyroidism in these patients. Hypothyroidism reappeared after potassium perchlorate withdrawal (76,77). Thyroid autoantibodies are common in patients with amiodarone-induced hypothyroidism, suggesting that these patients usually have an underlying autoimmune thyroid disease (75).

Other effects of amiodarone on the susceptible thyroid may be contributing or additive to iodine. Compared with iodine, amiodarone exhibits a potent and persistent inhibitory effect on TSH-stimulated cAMP production in FRTL-5 and JP26 Chinese hamster ovary (CHO) cells. The inhibitory effects of amiodarone occurred at lower concentrations of iodide than seen in sodium iodide-treated cells (78). Amiodarone induces cytochrome c release and apoptosis through an iodine-independent mechanism. When thyroid (TAD-2) and nonthyroid (HeLa) cells were treated with amiodarone both underwent apoptosis. Western blot analysis did not display variations in the expression of p53, Bcl-2, Bcl-XL, and Bax proteins during treatment with amiodarone and its main metabolite, desethylamiodarone (DEA). Generation of reactive oxygen species investigated by flow cytometry with dichloro fluorescein diacetate, did not show the production of free radicals during drug treatment of the cells (79). The latter suggests that the iodine content of amiodarone is not solely responsible for the observed apoptosis because sodium iodide-treated cells develop apoptosis through the generation of free radicals (80).

Mechanism of Maintenance of Hypothyroidism

The exact mechanism of iodine-induced hypothyroidism still remains elusive. From the findings described above, the following inferences concerning the inability of the predisposed thyroid to escape from the inhibitory effects of iodide can be drawn. After acute exposure to large doses of iodide the acute Wolff-Chaikoff effect supervenes. The initial load of iodide is largely rejected through an inhibition of the formation of iodothyronines and organic iodine. The inorganic iodine is therefore excreted by the kidneys. When the administration of iodide continues, the escape mechanism fails...
and therefore the inhibition of thyroid hormone synthesis continues. The intrathyroidal inorganic iodine concentration continues to be high, probably due to continued iodine uptake. It is unknown whether the downregulation of NIS as seen in the normal thyroid exposed to iodides operates in the thyroids of patients prone to iodine-induced hypothyroidism. The preformed intrathyroidal supply of thyronines is rapidly depleted, serum concentration of T4 and T3 decreases, serum TSH secretion increases, and the thyroidal iodine uptake continues uninhibited or actually increases, probably due to stimulation of NIS expression by TSH, further increasing the intrathyroidal iodine concentration. The inhibitory effects of iodine on the TPO regulation persists due to a decrease in TPO mRNA and this decrease may contribute to iodine-induced hypothyroidism. It must also be noted that the increased TSH cannot counteract the inhibitory effects of iodide on the proteolysis of Tg and the release of thyroid hormones, because the available intrathyroidal pool of thyroid hormones is greatly decreased.

There are many unanswered questions concerning the mechanism by which the diseased thyroid fails to adapt to long-term iodide excess. Large quantities of iodides, added to supernatants of human thyroid cells lines lead to excess molecular iodide generated by oxidation of iodine by the endogenous peroxidase and induces apoptosis in these cells through a mechanism involving generation of free radicals (80). It is not known whether the iodine-induced apoptosis contributes to chronic iodine-induced hypothyroidism.

The NIS protein expression pattern in the thyroid cells of patients with autoimmune thyroiditis is similar to normal thyroid tissue with the strongest NIS expression in the cells close to lymphocytic infiltrates (81). This may explain why NIS antibodies have been found in 20% and 80% of Hashimoto’s disease and Graves’ disease, respectively (82). It is possible that the downregulation of NIS expression by iodides observed in normal thyroid cells is defective in these cells because of the autoimmune process and, therefore, iodine continues to be taken up by the affected thyrocytes. Whether the NIS antibodies as well as the TPO and Tg antibodies contribute to iodine sensitivity in these susceptible individuals is not known.

Megalin (GP 330), a multiligand receptor on the apical surface of thyroid cells plays a role in trancytosis of Tg. It was found that megalin facilitates the transepithelial transport of thyroglobulin across thyrocytes resulting in diversion of Tg from lysosomal pathways and reduction of the extent of thyroid hormone release form internalized Tg molecules (83). Serum antibodies against megalin were found in 50% of patients with autoimmune thyroiditis (84). The role, if any, of these antibodies in the pathogenesis of iodine-induced hypothyroidism is not known.

Clinical and Laboratory Findings

The clinical picture of iodine-induced overt hypothyroidism is similar to that observed in ordinary primary hypothyroidism. Goiter may be present, a bruit may be heard on auscultation, and a metallic taste may occur because of an iodide effect on the gustatory function if the ingested quantities of iodides are high. The serum T4 and free thyroxine (FT4), are invariably low and serum T3 and free triiodothyronine (FT3) may be low, normal and occasionally increased, and serum TSH is invariably increased. The serum thyroglobulin and TPO antibodies are usually present in patients with underlying thyroid autoimmunity.

The radioactive iodine uptake is usually low, but in some patients normal or elevated values have been reported (28, 85). Thyroid ultrasound with color Doppler sonography may reveal normal or increased blood flow.

Treatment

It is readily apparent that a euthyroid patient who develops hypothyroidism when exposed to large quantities of iodides almost invariably returns to their previous thyroid state after iodide withdrawal. The time required for thyroid function to recover varies from 2 to 8 weeks, provided that the iodides are rapidly eliminated from the body. However, in patients treated with amiodarone, the time required may be prolonged due to the long half life of the drug. In most patients, the underlying cardiac disease precludes the discontinuation of amiodarone, and therefore, T4 replacement therapy must be carefully instituted simultaneously with the amiodarone treatment. Radiocontrast dyes used in the past for myelography, salpingography and lymphography (i.e., Lipiodol™, Guerbet, Cedex, France) may persist for months or years. Fortunately, these agents are rarely used today. The new radiocontrast dyes, i.e., diatrizoate meglumine sodium, iodothalamate, and meetrizamide are quickly cleared from the plasma and the affected thyroid recovers rapidly. However, thyroid hormone replacement therapy for a few months may be required in some patients.

It has to be emphasized that careful follow-up is required for all patients who developed transient iodine-induced hypothyroidism because many of them will eventually develop permanent hypothyroidism because of the underlying thyroid disease.

References

6. Raven MS 1949 The paradoxical effects of thiocyanate and of thyrotropin on the organic binding of iodine by the thyroid in the presence of large amounts of iodide. Endocrinology 45:296–304
46. Markou K, Paraskevopoulou P, Karaiskos M, Megrelli C,


53. Matsubayashi S, Mukuta T, Watanabe H 1998 Iodine-induced hypothyroidism as a result of excessive intake of Confectionery made with tangle weed, Kombu, used as a low calorie food during bulimic period in a patient with anorexia nervosa. Eating Weight Disord 3:50.


78. Pitsiavas V, Smerdely P, Boyages SC 1999 Amiodarone compared with iodine exhibits a potent and persistent inhibitory effect on TSH-stimulated c-AMP production in vitro: A pos-
83. Marino M, McCluskey RT 2000 Megalin-mediated transcytosis of thyroglobulin by thyroid cells is a calmodulin-dependent process. Thyroid 10:461–469.

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