



Iodine Effects on the Thyroid Gland: Biochemical and Clinical Aspects

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Introduction

Iodine is a critical element involved in thyroid gland function and thyroid hormone synthesis and secretion [1]. Thyroidal iodine uptake is tightly regulated by a specific thyroid hormone protein, the sodium-iodine symporter [2–6]. Subsequent to uptake into the thyroid gland iodine becomes incorporated into tyrosine and the resultant iodotyrosines are coupled into iodothyronines, such as L-thyroxine and L-triiodothyronine [7]. The number and position of the iodine molecules on thyronine help to determine its biologic activity. Comprehension of the important role of iodine in thyroid hormone physiology allows understanding of how iodine deficiency can cause goiter and hypothyroidism, and how iodine excess can cause either hypothyroidism or hyperthyroidism [8–10]. The purpose of this chapter is to review iodine physiology, its role in thyroid hormone function, and the potential beneficial and adverse effects of exogenous iodine on thyroid gland function.

Iodine Metabolism

Dietary iodine

Dietary iodine is ingested into the gastrointestinal tract and absorbed rapidly into the blood stream. An equilibrium is achieved between iodine intake and excretion in the urine [1,11]. Iodine is contained in a wide variety of foods, but processed flour, seafood and iodized salt, contribute the majority of iodine in a typical North American diet. The daily recommended allowance of iodine is considered to be 150 µg.

Sodium-iodide symporter

Once absorbed from the gastrointestinal tract, the iodine in the blood stream is actively concentrated in the thyroid gland because of the sodium-iodide symporter, a protein present on thyroid cell membranes [2–6]. Transport and concentration of iodide within the gland serves to maintain a thyroid:serum gradient of approximately 40:1. The iodide symporter has homology with thyroglobulin, thyroid peroxidase, and thyrotropin receptor [2], as well as with 11 other proteins, mostly of viral or bacterial origin, such as Streptococcus. This symporter is found in non-thyroidal tissues which also trap iodine from the circulation, such as salivary glands, gastric mucosa, and lactating mammary gland [3]. Patients with Graves' disease or Hashimoto's thyroiditis have circulating antibodies that recognize the symporter, although a functional clinical correlate has not been proven. Symporter antibodies from patients with autoimmune thyroid disease inhibit iodine uptake *in vitro* [4]. Perchlorate and thiocyanate decrease symporter activity in a dose dependent manner. Econazole, hexamethylene amiloride and dysidenin have been shown to be inhibitors of the symporter [5]. Increased radioiodine uptake correlates with increased expression of the symporter, and the latter is seen in the thyroid glands from patients with Graves' disease and autonomous nodules [6]. Mutations in the symporter have been identified in hypothyroid patients and are believed to be the cause of reduced iodine uptake, decreased thyroidal iodine content, and ultimately of diminished thyroid hormone synthesis [12].

Iodine kinetics

The amount of iodine concentrated by the thyroid gland depends upon the thyroid uptake and the amount of iodine already present within the thyroid gland. In

general, in North America, about 300–600 μg of iodine are taken into the gastrointestinal tract daily and approximately 100–200 μg are trapped by the thyroid gland. This iodide becomes organified, incorporated into tyrosine and the resultant iodotyrosines are coupled into iodothyronines. Most of the iodine within the thyroid gland is stored within thyroglobulin and a total amount of about 5000–10,000 μg of iodine is contained within the normal thyroid gland. This large amount of stored iodine serves as a reservoir for providing iodine to sustain thyroid hormone production even in periods of relatively low iodine intake. Normally, most of the iodine in blood circulates as hormonal iodine. The iodothyronines are secreted as 3, 5,3',5'-tetraiodothyronine (thyroxine; T4) and 3,5,3'-triiodothyronine (T3). T4 and T3 represent the major active thyroid hormones and are responsible for virtually all thyroid hormone action. Reverse T3 (3,3,5'-triiodothyronine) and lesser iodinated forms of thyronine, such as 3,5-diiodothyronine and 3',5'-diiodothyronine, are also secreted but have limited biologic activity [13].

Iodine leak is a process by which the thyroid gland regulates intrathyroidal iodine content by secreting unbound iodine into the blood stream. Intrathyroidal iodide represents to a large degree unbound non-organified iodine that was most recently trapped by the thyroid gland [14]. Circulating iodine, usually bound to a thyronine molecule, is excreted mostly by the kidney although a smaller amount is excreted via the liver and subsequently the gastrointestinal tract. The kinetic aspects of iodine dictate that a 24 hours urine sample generally reflects dietary intake, as about 97% of dietary intake is excreted in the urine and the remaining 3% is excreted in the gastrointestinal tract [1]. Renal iodine is passively reabsorbed and, therefore, depends upon the glomerular filtration rate. Clinically, the iodine content of a 24 hours urine can be easily determined as a reflection of dietary (or exogenous) intake. In the United States, a euthyroid individual will excrete about 300–800 μg of iodine daily. Although it is believed that any normal subject can develop an iodine deficient goiter following severe, chronic iodine restriction, there probably are other factors that play a role in this process, most notably a genetic predisposition. Patients with severely restricted dietary intake and who may be susceptible to develop an iodine deficient goiter generally take in and excrete less than 50 μg iodine daily.

The T4 and T3 molecules contain 66% and 58% iodine by weight, respectively, and approximately 90–100 μg of iodine is secreted by the thyroid gland daily (90 μg T4, 7 μg T3 and several micrograms from lesser iodinated substances) [1]. Iodide in the serum circulates bound to proteins or thyronines and in an unbound form. Therefore, about 100–150 μg of iodine must be taken in

daily to maintain normal thyroid function over a prolonged period of time. A normal thyroid gland traps about 10–30% of ingested iodine daily, but this fractional thyroidal uptake of iodide will increase when dietary iodine is deficient. As noted, thyroidal iodine uptake varies inversely with increasing serum iodine concentration, whereas renal excretion appears independent of serum iodide concentration.

There is a surfeit of iodine in the typical average North American diet secondary to intake of processed flour (with iodate preservatives), iodized salt and seafood [15,16]. Other substances that contain large amounts of iodine include kelp (seaweed), various dietary supplements, radiocontrast agents (e.g., for IVP, cardiac catheterization), and amiodarone. Some water purification systems utilize iodine and some antiseptics contain iodine (e.g., Betadine, iodoform gauze). The amount of iodine actually absorbed from these topical iodine containing materials will vary depending upon the concentration of iodine in a particular agent, the amount applied and on the extent of dermal injury.

Radioisotopic iodine

Radioisotopic iodine is used clinically to assess thyroidal iodine uptake. Typically, 123-I is used although 131-I was used more frequently in the past. 123-I has only beta emissions which allow quantitation by isotopic detectors but have minimal destructive effects [17]. 131-I produces both beta and gamma emissions. As a result, 123-I is preferred for diagnostic purposes and 131-I is used to treat thyroid cancer and hyperthyroid patients. The physical half life of 123-I is about 12 hours and for 131-I about 7 days, although the biologic metabolism of these agents is more rapid and depends on the thyroid functional state. It is correct to assume that radioisotopic iodine, e.g., 123-I, is treated by the body comparably to the non isotopic form of iodine, 127-Iodine. Radioactive iodine should not be given to pregnant patients as it can cross the placental barrier and be trapped by the fetal thyroid gland.

Clinical Effects of Iodine

Radiocontrast agents

Radiocontrast agents that are used for certain radiologic procedures, for example, cardiac catheterization, intravenous pyelograms, CAT scans and myelograms, contain a large amount of iodine, approximately 200,000–300,000 μg [18–21]. These agents are used to enhance the visualization of vascular or anatomic structures. MRI studies use gadolinium which does not contain iodine. These radiocontrast agents release their iodine after injection and it rapidly becomes available for thyroidal

uptake. Patients with underlying, perhaps mild, autoimmune thyroid disease, such as Hashimoto's thyroiditis, are particularly susceptible to develop abnormal thyroid function over the ensuing several weeks after exposure [22,23]. Iodine exposure in these patients most typically causes hypothyroidism although more rarely hyperthyroidism may become manifest. Abnormal thyroid function may persist for many months or may be relatively transient. These effects may have significant clinical implications, especially in older individuals with other medical conditions. The radioactive iodine uptake test becomes impossible to reliably assess following radiocontrast dye administration. Patients with non-autoimmune goiters also are prone to develop thyroid dysfunction following exposure to radiocontrast dyes. It is controversial whether completely normal subjects also may develop perturbed thyroid function tests in this circumstance; we believe the evidence suggests this does occur but is less common than in patients with preexisting thyroid abnormalities [24]. Serum iodine concentrations remain markedly elevated for as long as several months after exposure to radiocontrast dyes. Most radiocontrast dyes also exert a separate effect on thyroid gland function in that they inhibit T4 to T3 conversion. The radiocontrast agents possess this property to a differing degree, but Iodate (Oragrafin) is perhaps the most effective in this regard, and it even is utilized as an antithyroid agent to treat hyperthyroid subjects [25].

The thyroid gland is capable of autoregulating iodine uptake such that the fractional thyroidal iodine uptake is decreased after a subject has been exposed to radiocontrast dye. This capacity of the thyroid gland may help explain why abnormal thyroid function tests are rarely observed in patients given radiocontrast dyes, especially given the frequency with which these procedures are performed. Nevertheless, the clinician should be alert to this possibility, especially in a patient with underlying thyroid disease. Further studies are needed to assess the frequency of perturbations in thyroid function tests following exposure to radiocontrast dyes as well as the length of time that radiocontrast dyes will alter radioiodine uptake.

Iodine containing agents

Numerous medications and agents contain significant amounts of iodine (Table 1). In addition to radiocontrast agents, topical iodine preparations, such as Betadine contain about 10 mg/ml of solution. Topical agents may get absorbed especially if used repetitively and when applied to denuded skin or to mucous membranes. Ophthalmic solutions, e.g., echothiophate iodide and idoxuridine contain approximately 20–40 µg per drop. Quadrinal, vitamins and iodochlorhydroxyquin contain significant amounts of iodine. Kelp may be ingested as an

organic, supplemental food product; kelp tablets contain approximately 150 µg iodine. We suggest that patients with known thyroid disease avoid these agents.

There are many other agents or compounds that contain iodine and it is difficult to know with certainty when they might influence thyroidal uptake or function. We suggest that a thorough history be taken and that urine iodine be measured when it is relevant that iodine status be determined clinically. A 24 hours urine iodine greater than about 1000 µg will reflect a degree of iodine excess which is likely to have affected thyroidal homeostasis.

Amiodarone

Amiodarone is a commonly used anti-arrhythmic agent. A 200 mg tablet of amiodarone contains 75 mg of iodine which will be released after ingestion [26–29]. Amiodarone has varied effects on thyroid function, one of which is to decrease T4 to T3 conversion. In addition, and probably because of its iodine content, amiodarone can cause hyperthyroidism or hypothyroidism. Typically, hyperthyroidism is more common in iodine deficient areas and hypothyroidism predominates in areas of iodine sufficiency [26–29]. The onset of thyroid dysfunction usually occurs several weeks or months after the medication is instituted, and the altered thyroid function may persist after the medication is discontinued. Amiodarone is stored in fat and is slowly released such that serum levels persist for many months following discontinuation of the medication. There are two mechanisms by which amiodarone causes thyrotoxicosis [26–29], and these have been designated as Type 1 or Type 2 amiodarone-induced thyrotoxicosis. Type 1 refers to the situation in which amiodarone causes direct thyroidal injury and thyroiditis, with subsequent release of stored thyroid hormones. IL-6 is elevated in the serum as a marker of the inflammatory process. This type of hyperthyroidism generally abates as the amount of stored thyroid hormones available for release is diminished. The radioactive iodine uptake test shows a very low (less than 1%) value during the hyperthyroid phase of this disease. As in subacute thyroiditis, there may be evolution through a euthyroid and hypothyroid phase prior to restoration of euthyroidism. The severity of the illness and requirement for therapy will vary in different patients, but corticosteroids may be a useful adjunctive therapeutic agent. Type 2 amiodarone induced thyrotoxicosis is a form of iodine induced hyperthyroidism and is presumed to be related to the iodine contained within the amiodarone molecule. The treatment of this disorder is to discontinue the amiodarone if possible, although it is recognized that the effects on the thyroid gland may persist for several months. Type 2 amiodarone-induced hyperthyroidism should be treated with antithyroid agents (either propylthiouracil or methimazole) and

Table 1. Iodine content of iodinated radiocontrast dyes and iodine containing compounds

| Substance | Iodine content | Typical dose | Total dose of iodine (mg) |
|--|------------------------------|------------------------------|----------------------------|
| <i>Radiocontrast dyes</i> | | | |
| Cholestagraphic (e.g. Iopodate) | 55–70% | 3–9 g | 1650–6300 |
| Radiologic (e.g. IVP, angiogram, CT) Diatrozoate, iodamide | 45–60% | 1–70 g | 450–4200 |
| Lymphangiogram (e.g. Lipoidal) | 45–60% | 1–70 g | 450–4200 |
| Myelogram (e.g. Metrizamide) | 48% | 5–15 ml | 1100–3000 |
| <i>Iodine containing drugs</i> | | | |
| <i>Oral Agents</i> | | | |
| Amiodarone | 75 mg/200 mg | 300–1200 mg (initial) | 75–300/d |
| Cough Medications (e.g. Potassium iodide, iodinate glycerol) | 15–325 mg/tsp | 1–2 tsp q 4 hours | 90–3900/d |
| Antiamebic (e.g. iodochlorohydroxyquin) | 104 mg/tablet | 600–650 mg tid x 20d | 312/d |
| Quadrinal (KI) | 320 mg/tablet 160 mg/5 ml | 1 tab qid 10 ml q 4 hours | 1280–1920/d 1280–1920/d |
| Kelp Tablets | 0.15 mg/tab | 1–3 /d | 0.15–0.45/d |
| <i>Antithyroid Agents</i> | | | |
| Lugols solution | 8.4 mg/drop | 15 drops qid | 378/d |
| SSKI | 38 mg/drop | 5 drops qid | 760/d |
| <i>Topical Iodine</i> | | | |
| Povidone iodine (Betadine) | 10 mg/ml | 1–10 ml | 10–100 |
| Ophthalmic Solution (e.g. Idoxyuridine) | 18 µg/drop | 2 drops qid | 0.144/d |

Drop size varies with the dropper used. Only specific compounds are depicted in this table and other solutions and compounds exist that also contain iodine. Table adapted from Chapter 37, Adverse Effects of Iodine by Nuovo JA and Wartofsky L in *Principles and Practice of Endocrinology and Metabolism*, Second Edition, Editor, KL Becker, J.B. Lippincott Co, Philadelphia, PA, 1995.

beta blockers. Perchlorate inhibits iodine uptake by the thyroid gland and this agent can be used (with caution because of its potential toxicity to bone marrow) to treat this type of hyperthyroidism.

Notwithstanding the distinctions drawn between these two classic descriptions of amiodarone induced thyrotoxicosis, it is our experience that many patients will have an overlap between Type 1 and Type 2 disease. Consequently, we suggest considering a combined treatment approach with steroids, antithyroid agents, and perchlorate. Amiodarone induced thyrotoxicosis is usually difficult to treat. Indeed, the diagnosis itself may be problematic since the patients have associated cardiac disease which may cause palpitations and other symptoms and signs that also occur in hyperthyroidism. Proper interpretation of thyroid function tests is important. The radioactive iodine test is low and not particularly helpful. Total and Free T4 may be elevated in hyperthyroid or euthyroid patients since amiodarone inhibits T4 to T3 conversion and, as a result, T4 clearance is decreased and T4 levels increase.

Therefore, an elevated total or free serum T3 is probably the best marker for the presence of thyrotoxicosis since it is typically low in euthyroid individuals receiving the drug due to impaired T4 to T3 conversion. Because these patients are systemically ill with cardiac disease, their thyroid function tests may trend toward the profile seen in non thyroidal illness in which a low serum T3 would be expected secondary to inhibition of T4 to T3 conversion. Therefore, even a normal T3 may be considered inappropriately high.

Iodine excess

Following ingestion or exposure to large single doses of iodine (in the milligram range) there is acute inhibition of the peroxidase enzyme which inhibits the conversion of iodide to iodine resulting in diminished T3 and T4 generation.

Iodide induced thyroid dysfunction and goiter

Chronic excessive iodine exposure can result in goiter, although the majority of such patients are euthyroid [30].

Occasionally, patients will develop iodine induced hypothyroidism or hyperthyroidism [22–24]. The frequency of these events is unknown and it is believed that iodine induced thyroid hypofunction occurs most frequently in patients with underlying autoimmune thyroid disease who are unable to organify iodine normally. The inhibition of organification during excess iodine exposure is called the Wolff-Chaikoff effect [31,32]. Normally, individuals are able to escape from this decreased organification and resume relatively normal thyroid synthetic ability. Patients who develop iodine induced goiter and dysfunction are thought to be unable to escape from this effect normally. A recent study suggests that there is diminished symporter mRNA expression with a resultant decrease in activity during the escape from the Wolff-Chaikoff effect [10]. Typically, it requires many weeks of iodine exposure to develop thyroid dysfunction. Pregnant women should avoid excessive iodine exposure since iodine readily crosses the placental barrier and the fetus may develop a goiter. Indeed, a fetus exposed to excessive iodine may manifest an extremely large goiter that may cause dyspnea and even asphyxiation. Lugol's solution and SSKI should not be given to pregnant women except in extremely unusual situations in which case the fetus should be monitored with thyroid or neck ultrasound examinations; moreover iodine administration in these circumstances should be short term.

Iodine treatment of hyperthyroidism

Thyrotoxic patients may be treated with antithyroid agents. Propylthiouracil or methimazole decreases intrathyroidal hormonal synthesis and the former agent inhibits T4 to T3 conversion [33]. Beta blockers decrease the peripheral manifestations of excessive thyroid hormones but do not affect the thyroid gland. In selected circumstances, iodine containing agents, such as Lugol's solution or SSKI, can be used to treat a thyrotoxic patient. We believe that these agents should be used sparingly and only after the previous use of methimazole or propylthiouracil. Iodine administration can have divergent effects. When administered for a short time period, e.g. 1–2 weeks, they inhibit T4 and T3 secretion. Employing a radioisotopic analysis, we were able to assess thyroidal secretion directly and demonstrate that exogenous SSKI decreased thyroidal secretion such that serum T4 and T3 concentrations fell by approximately 50% over a 10–14 day time period [34]. This pronounced beneficial effect of SSKI or Lugol's solution represents the reason why it is considered an effective antithyroid agent. On the other hand, when SSKI or Lugol's solution is continued for at least several weeks, the adverse effects of iodine then can become predominant. In this circumstance, prolonged

iodine exposure increases thyroidal iodine content and there is escape from the iodine-induced inhibition of organification [35]. Unabated thyroid hormone synthesis and secretion ensues, resulting in a type of hyperthyroidism that is especially difficult to treat with conventional means because of the enhanced intrathyroidal iodine fuel source.

Iodine exacerbation of existing hyperthyroidism responds poorly to the use of methimazole or propylthiouracil. Because of these considerations, the clinician should reserve use of SSKI or methimazole to those hyperthyroid patients that are thought to have severe thyrotoxicosis, perhaps in thyroid storm, or in patients that need to be rendered euthyroid prior to surgery, since the duration of exposure to excessive iodine will be limited. Some clinicians also will use SSKI or Lugol's solution to render a patient euthyroid after therapeutic administration of radioactive iodine [36]. The radioactive iodine may take 2–3 months to produce hypothyroidism and the SSKI or Lugol's solution is started several days after ¹³¹I administration and continued for 2–3 weeks. Iodine will cause the patient to more rapidly become euthyroid presumably because of inability to escape from the Wolff-Chaikoff effect related to the radiation-induced damage to the gland. We think this regimen is reasonable in selected patients after a therapeutic dose of radioactive iodine, but is risky otherwise since the SSKI or Lugol's solution might exacerbate hyperthyroidism. In either case, these patients must be followed carefully with frequent thyroid function tests.

Iodate (Oragrafin) is a cholecystographic radiocontrast agent that also can be used to treat certain patients with hyperthyroidism [37–40]. Iodate contains iodine which is released after absorption and which then inhibits thyroid hormone secretion. In addition, the Iodate molecule itself inhibits T4 to T3 conversion. As a result, the administration of Iodate to a hyperthyroid patient is associated with about a 50% decrease in T3 concentration, an effect noted within 24–48 hours and which persists for several days or weeks. The typical dose of Iodate to a hyperthyroid patient is 0.5–3.0 grams every 2–3 days. We prefer that Iodate only be utilized clinically in similar situations in which we recommended SSKI or Lugol's solution (see above). Iodate has been given for prolonged periods of time, up to 6–12 months, with observation of resultant iodine induced hyperthyroidism only infrequently. However, individual cases of Iodate induced hyperthyroidism have been reported. We speculate that the frequency of Iodate induced hyperthyroidism is less common than with SSKI or Lugol's solution because of the additional antithyroid effect that Iodate possesses of inhibiting T4 to T3 conversion. Further studies are needed to fully

understand the pharmacokinetics of Iodate in hyperthyroid patients. Like stable iodine, it also should not be used in pregnant women.

Iodine and autoimmunity

There may be an association between the development of autoimmune thyroid disease and exposure to iodine. Animals develop lymphocytic thyroiditis more frequently when exposed to excessive iodine and the generation of thyroid antibodies appears to be more frequent in this circumstance. Bagchi et al. [39] assessed the role of thyroidal injury in the development of iodine induced thyroiditis in an obese chicken model. In this model, iodine exposure causes thyroiditis whereas iodine depletion prevents lymphocytic infiltration of the thyroid gland. Thyroglobulin tolerization early in life helped reduce the iodine associated thyroiditis, as did treatment with ethoxyquin, an antioxidant. The precise mechanism by which iodine causes thyroiditis is unknown but could relate to the fact that thyroglobulin that is enriched with iodine seems more immunogenic. In the nonobese diabetic mouse, increased iodine intake has also been shown to increase the frequency and extent of thyroiditis [40]. CD4 and CD8 T cells are required for this process.

TSH induces expression of the sodium-iodide symporter, thyroid peroxidase, and thyroglobulin genes by modulating the activity of thyroid specific transcription factors, e.g., TTF1, TTF2 and Pax-8 [41], Thyroglobulin counter-regulates this TSH induced protein increase by decreasing expression of specific transcription factors. This homeostatic effect of thyroglobulin requires further study, especially as it relates to the iodination of thyroglobulin and subsequent autoimmunity. Another exciting recent discovery relates to the identification of megalin, a multiligand receptor, on the apical surface of thyroid cells [42]. Megalin antibodies have been found in Heymann nephritis and Marino et al. [42] recently found that 50% of patients with autoimmune thyroiditis and 10% of patients with Hashimoto's thyroiditis had serum megalin antibodies. Further studies need to be performed to investigate the relationship of these antibodies to thyroglobulin iodine content.

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