EFFECTS OF IODINE ON THYROID FUNCTION IN MAN*,**

LEWIS E. BRAVERMAN[1]

WORCESTER

INTRODUCTION

Iodine is required for the synthesis of the thyroid hormones, thyroxine (T_4) and triiodothionone (T_3). Ambient iodine intake derives primarily from dietary food (Table 1) and water.

The United States and Canada, the United Kingdom, Japan, and many areas of Scandinavia are iodine-sufficient. From recent but incomplete studies in the United States, the average iodine intake is approximately 220 μg daily. In contrast, most of continental Western Europe is mildly iodine-deficient with intake varying from 40 to 100 μg iodine daily.

The use of iodine-containing drugs and nature food products (Table 2) supplies pharmacologic amounts of iodine to large numbers of individuals. Certainly, many of these patients require these medications to treat a wide variety of illnesses.

EFFECTS OF IODINE ON THYROID FUNCTION (1)

Although required for thyroid hormone synthesis, excess intrathyroid iodide can paradoxically decrease the organification of iodide and subsequent hormone synthesis, a phenomenon first described *in vivo* in the rat by Wolff and Chaikoff in 1948 and termed the "acute Wolff-Chaikoff effect" (2). The iodide-induced decrease in hormone synthesis is transient, however, and thyroid hormone synthesis resumes in spite of continued excess iodine administration. This latter phenomenon apparently serves to defend the thyroid from iodine-induced hypothyroidism and goiter and has been termed the "adaptation or escape" from the "acute Wolff-Chaikoff effect" (3). The mechanism for this escape appears to be a marked reduction in the active transport of iodide from the plasma into the thyroid follicular cell, thereby reducing the high intrathyroid iodide content and permitting the resumption of normal thyroid hormone synthesis (4). Although this inhibitor of the iodide transport process appears to be an organic iodine-containing compound, it has not as yet been fully identified.

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* Division of Endocrinology and Metabolism, University of Massachusetts Medical School, Worcester, MA 01655.

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[1] Address reprint requests to: Dr. Lewis E. Braverman, University of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA 91655.

TABLE 1
Iodine Rich Foodstuffs

Food	Iodine Content/Average Serving (μg)
Bread	190 or 170
Cod	102
Milk	52
Shrimp	27
Eggs	18
Perch	14
Canned tuna	12

Iodine administration may also affect thyroid gland function by decreasing thyroid hormone release in both euthyroid and hyperthyroid patients. In the former, excess iodine results in subtle decreases in serum T_4 and T_3 concentrations and a compensatory increase in the serum TSH concentration, all values well within the normal range (5). In the hyperthyroid patients, iodine is useful adjunctive therapy in the treatment of thyroid storm and in preparing patients for thyroid surgery.

IODINE INDUCED HYPERTHYROIDISM (TABLE 3)

An increase in the incidence of hyperthyroidism following the use of iodides to treat endemic iodine-deficient goiter was first reported in 1820 by Coindet. Breuer and Kocher more carefully documented this syndrome, and the term Jodbasedow was employed by European investigators. Similar trials of iodide followed in the United States in the 1920's and a sharp increase in hyperthyroidism was noted. Iodate used in the manufacture of bread in Holland was associated with an increased incidence of hyperthyroidism. Since this latter report, iodide-induced hyperthyroidism has frequently followed iodide repletion in many endemic iodine-deficient areas of the world.

Reports from Belgium, France and Germany emphasize the frequency of iodine-induced hyperthyroidism in many areas of continental western Europe where iodine intake is marginal or low. As noted in Table 2, many iodine-containing drugs are available and most have been incriminated in the etiology of iodine-induced hyperthyroidism. The half lives of these drugs range from 0.4 days for iodide to approximately 100 days for amiodarone. Although most patients who develop Jodbasedow have nodular goiters, solitary autonomous goiters or underlying Graves' disease, some have apparently normal thyroids. These observations strongly suggest that the strikingly greater incidence of iodine-induced hyperthyroidism observed in continental Western Europe than in the United

TABLE 2
Commonly Used Iodine Containing Drugs

Oral or local agents	Iodine Content
Amiodarone	75 mg/tab
Benziodarone*	49 mg/100 mg tab
Calcium iodide (e.g., Calcidrine Syrup)	26 mg/ml
Diiodohydroxyquin (e.g., Yodoxin)	134 mg/tab
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/tab
Iodine containing vitamins	0.15 mg/tab
Iodinated glycerol (e.g., Organidin)	15 mg/tab 25 mg/ml
Idoxuridine ophthalmic solution (e.g., Herplex)	18 μg/drop
Isopropamide iodide (e.g., Darbid, Combid)	1.8 mg/tab
Kelp	0.15 mg/tab
KI (e.g. Quadrinal)	245 mg/tab 24 mg/ml
Lugol's Solution	6.3 mg/drop
Niacinamide hydroiodide + KI (e.g., Iodo-Niacin)	115 mg/tab
Ponaris (e.g. Nasal Mucosal Emollient)	0.6%
SSKI	38 mg/drop
Parenteral Preparations	
Sodium Iodide, 10% solution	85 mg/ml
Topical antiseptics	
Diiodohydroxyquin cream (e.g., Vytone)	6 mg/gm
Iodine Tincture	40 mg/ml
Iodochlorhydroxyquin cream (e.g., Vioform)	12 mg/gm
Iodoform gauze (e.g., Nugauze)	4.8 mg/100 mg gauze
Providone iodine (e.g., Betadine Solution)	10 mg/ml
Radiology contrast agents	
Diatrizoate meglumine and sodium (e.g., Renografin-76)	370 mg/ml
Iodized oil	380 mg/ml
Iopanoic acid (e.g., Telepaque)	333 mg/tab
Ipodate (e.g., Oragrafin)	308 mg/cap
Iothalamate (e.g., Angio-Conray)	480 mg/ml
Metrizamide (e.g., Amipaque)	483 mg/ml before dilution

* Not FDA Approved

TABLE 3
Iodine Induced Hyperthyroidism

I. Iodine supplementation for endemic iodine deficiency goiter.
II. Iodine administration to patients with euthyroid Graves' disease especially when in remission after antithyroid drug therapy.
III. Iodine administration to patients with underlying thyroid disease. More common in areas of marginal iodine intake than in areas of iodine sufficiency.
  A. Nontoxic nodular goiter
  B. Autonomous nodule
  C. Nontoxic diffuse goiter
IV. Iodine administration to patients with no recognized underlying thyroid disease, especially in areas of mild to moderate iodine deficiency.

Kingdom, the United States, and Japan is due to iodine deficiency since iodine intake is more than sufficient in these latter three areas.

It should be emphasized, however, that iodine-induced hyperthyroidism can occur in areas of iodine sufficiency, especially in patients with underlying nodular or diffuse nontoxic goiters (perhaps underlying Graves' disease). Pharmacologic doses of iodide (180 mg/day) were administered to eight patients with nontoxic nodular goiter residing in Boston, an area of adequate iodine intake; clinical and laboratory evidence of thyrotoxicosis developed within weeks in four of these patients and became more severe after iodide was withdrawn (6). The etiology of thyrotoxicosis in these patients remains obscure. Although TRH or thyroid suppression tests were not done before iodide administration, some patients with nontoxic nodular goiter and normal serum T_4 and T_3 concentrations fail to respond to TRH, and others may have abnormal suppression tests. In the foregoing series, one of the four patients who developed hyperthyroidism failed to respond to TRH two years after iodides were discontinued, in spite of normal serum T_4 and T_3 concentrations. Thus, some of the patients who develop iodide-induced hyperthyroidism might have had autonomous thyroid function without overt hyperthyroidism. Jodbasedow has also been reported in other patients residing in the United States (7).

The pathogenesis of iodine-induced hyperthyroidism is unclear but may relate to prior intrathyroid iodine content, since iodine-induced hyperthyroidism is far more common in areas of iodine deficiency. It is reasonable to assume, therefore, that the iodine-deficient gland may become hyperfunctioning when sufficient iodine substrate is supplied for hormone synthesis. In addition, areas of autonomous thyroid function probably exist in many nontoxic multinodular goiters, irrespective of iodine intake. Exposure of these autonomous areas to a large quantity of iodine may enhance thyroid hormone synthesis and release due to a

failure of the normal autoregulatory mechanisms whereby normal thyroid function is maintained in the presence of excess plasma iodide. It is also possible that areas of iodine-poor thyroglobulin are present in the multinodular goiters in patients residing in iodine-sufficient areas, and that exposure of this abnormal thyroglobulin to large quantities of iodine results in excess thyroid hormone synthesis.

IODINE INDUCED HYPOTHYROIDISM (TABLE 4)

Patients with underlying thyroid disease may develop hypothyroidism due to a failure to escape from the acute Wolff-Chaikoff effect. Although the exact etiology of the hypothyroidism is not certain, it is likely that these patients have an underlying subtle defect in the organification of iodide and subsequent hormone synthesis. Thus, an intrathyroidal concentration of iodide which normally would not impair the oxidation of iodide sufficiently to decrease hormone synthesis does so in these patients. The defect in the intrathyroid organification of iodide is best detected by a positive iodide (^{123}I)-perchlorate discharge test which is often positive in those patients who do develop iodide induced hypothyroidism.

Euthyroid patients treated years before for Graves' disease with radioactive iodine or surgery (8) and euthyroid patients with Hashimoto's thyroiditis (9) frequently develop iodide induced hypothyroidism. Pa-

TABLE 4
Iodine-Induced Hypothyroidism

I.	Underlying thyroid disease
	A. Hashimoto's thyroiditis
	B. Euthyroid patients previously treated for Graves' disease by ^{131}I or thyroidectomy
	C. Primary subclinical hypothyroidism, especially in the elderly
	D. After transient post-partum thyroiditis
	E. After subacute, painful thyroiditis
	F. Posthemithyroidectomy for benign nodules
II.	No underlying thyroid disease
	A. Cystic fibrosis
	B. Chronic lung disease (Hashimoto's thyroiditis was not ruled out)
	C. Chronic non thyroidal illness (rare)
	D. Elderly subjects (rare)
III.	Iodine plus other potential goitrogens
	A. Lithium
	B. Sulfisoxazole: cystic fibrosis
IV.	Fetus and neonate, mostly preterm: secondary to transplacental passage of iodine and exposure of newborns to topical or parental iodine-rich substances.

tients who were previously treated for a benign thyroid nodule by a lobectomy may also develop hypothyroidism due to excess iodine ingestion (10), although this observation has not been consistently observed (11). Very recently, we have observed that euthyroid patients with a previous episode of subacute thyroiditis (11) or post partum silent thyroiditis (12) not infrequently develop iodide induced hypothyroidism. In both groups of patients the iodide-perchlorate discharge test was frequently positive (11, 13).

Occasionally, patients without confirmed underlying thyroid disease, such as those with cystic fibrosis or chronic lung disease, may develop hypothyroidism during ingestion of iodine containing expectorants, such as Organidin (14). There is also synergism of iodine with other mild goitrogens, especially Lithium, resulting in hypothyroidism.

The fetus is inordinately sensitive to the blocking effects of iodine on thyroid hormone synthesis, resulting in fetal and newborn transient hypothyroidism often associated with goiter. Since iodides readily cross the placenta, the administration of large quantities of iodine to pregnant women has resulted in hypothyroidism in the newborn. Iodine is actively transported by the breast and secreted into the milk, and the administration of iodine to the nursing mother could result in iodine-induced goiter and hypothyroidism in the infant.

Iodine readily crosses the vaginal mucosa and vaginal douching in nonpregnant women with povidone iodine (PVP-I) for 2 weeks increased the serum iodide concentration, resulting in small increases in the serum TSH concentration (15). Over the past few years, it has been reported that the use of PVP-I vaginal preparations during the last trimester and during labor (16), or topical application of PVP-I to the skin of newborns, results in transient hypothyroidism in the newborn as indicated by an elevation in serum TSH. Premature infants are particularly at risk. Studies in the rat strongly suggest that escape from the acute inhibitory effect of iodine on thyroid hormone synthesis occurs in the late neonatal period which corresponds to the last few weeks of term human fetal life (17).

It is of interest that the vast majority of studies demonstrating transient perinatal hypothyroidism secondary to excess iodine exposure emanate from continental western Europe where mild to moderate iodine deficiency is present. Whether this is due to the iodine deficiency or to the greater use of iodine containing medications during pregnancy and the perinatal period is not known. Since the fetus and neonate appear to be at greater risk than adults to develop iodine induced thyroid hypofunction, it is advisable to avoid iodine containing medications during this vulnerable period.

AMIODARONE IODINE INDUCED THYROID DISEASE

Amiodarone, a benzofuranic derivative containing 37.2% iodine (75 mg of iodine per 200 mg tablet), is widely used for the long-term treatment of cardiac arrhythmias and angina pectoris. Its half-life in humans is reported to vary from 5 to 100 days, and approximately 9 mg of free iodine is released daily during the metabolism of a daily 300 mg dose. Amiodarone is also a potent inhibitor of the phenolic or outer ring deiodination (5′-deiodinase) of T_4 and reverse T_3. This inhibition results in both decreased production of T_3 from T_4, causing a reduction in the serum T_3 concentration, and decreased deiodination of reverse T_3, resulting in an elevated serum reverse T_3 concentration. The serum T_4 and free T_4 concentrations are also frequently elevated during amiodarone therapy.

In addition to the effects of amiodarone on the peripheral metabolism of the thyroid hormones and on pituitary TSH secretion, a major complication of therapy is the relatively high frequency of iodine-induced thyroid dysfunction. The type of iodine-induced thyroid dysfunction appears to be related to the ambient environmental iodine intake prior to amiodarone administration (18). As noted above, iodine-induced hyperthyroidism is more common in areas of low or marginally low iodine intake such as continental Western Europe and occurs in approximately 10 percent of patients residing in this area. Hyperthyroidism in these patients is best confirmed by an elevation in the serum T_3 and free T_3 concentrations and the serum SHBG concentration. In contrast, amiodarone iodine-induced hypothyroidism is far more common in the United States, where iodine intake is sufficient, occurring in approximately 20 percent of patients in our retrospective study (18). Many of the patients who develop hypothyroidism have positive thyroid anti-microsomal antibodies and it is well recognized that Hashimoto's thyroiditis predisposes to the development of iodine-induced hypothyroidism. Hypothyroidism is best diagnosed in these patients by an elevated serum TSH concentration.

In view of the high incidence of iodine-related thyroid dysfunction associated with amiodarone administration, the drug should be given with caution in patients with pre-existing goiter or history of thyroid disease. Careful pre-drug thyroid testing, including thyroid antibodies, should be done and thyroid function tests carried out every 6 months or sooner should the patient develop symptoms of hyper- or hypothyroidism. Amiodarone-associated hyperthyroidism is often resistant to standard antithyroid drug therapy when goiter is present. Amiodarone should almost always be immediately discontinued. Corticosteroids have been

recommended in addition to the antithyroid drugs, especially in those patients in whom amiodarone induced subacute thyroiditis may occur. We have proposed to treat this disorder with PTU or methimazole and perchlorate (1 gm daily) for the first 30–40 days (19). The latter drug blocks the thyroid iodide trap thereby decreasing the intrathyroid iodine content. No toxicity was observed using this combination of drugs and the hyperthyroidism improved more rapidly. Others have suggested that a subtotal thyroidectomy can be safely carried out in selective patients in order to terminate the resistant and life threatening hyperthyroidism (20, 21). We have recently carried out a near total thyroidectomy in a drug resistant, precarious cardiac patient with rapid restoration of euthyroidism and re-institution of amiodarone therapy (22). The hypothyroidism associated with amiodarone is easily treated with L-thyroxine or L-triiodothyronine therapy.

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DISCUSSION

Mulrow (Toledo): There is another group of patients in whom we occasionally see hypothyroidism when given iodine as those who have been radiated for say, lymphomas in the neck, and then get various CAT scans, etc., then become hypothyroid. Have you noticed that as problem?

Braverman: Yes, there are patients who have received high voltage radiation therapy to the head and neck for malignant disease. If you follow these patients over the next five years, approximately 80 percent will become hypothyroid on their own. I suspect that the process will be accelerated in those who receive the large amounts of exogenous iodine.

Field (Boston): I'd like to compliment you on this very comprehensive presentation on the multifaceted effects of iodine on thyroid metabolism. In *in-vitro* studies, its been possible to show that iodine will inhibit some of the biochemical events in the thyroid, and these can be prevented if one can abolish the organification of iodide with the use of propylthyurocil or methimazole. Do you know whether the Wolff-Chaikoff effect in man or animal can be prevented by the concomitant administration of propylthiouracil?

Braverman: I think that, in the rat, one can essentially block that 48 hour window. These are old studies showing that the administration of compounds such as propylthiouracil and methimazole which block organification. Its odd that the inhibitor of hormone synthesis secondary to excess iodine injection, believe it or not, has not as yet been identified, and there is some feeling that it may be a phospholipid, but it is very unclear. I suppose that in the near future, with the explosion of molecular biology techniques, this might very well become known.

Asper (Baltimore): A fine lucid review, Lew. You spoke of hypothyroidism as being induced in infants of mothers who receive iodine. Do not some of those infants have huge goiters at birth, and obstructive symptoms?

Braverman: Yes, an occasional newborn will be born with a huge goiter and hypothyroidism, and as a matter of fact, some of the earlier reports in the 1920's and 1930's, some

of the largest goiters reported in newborns were secondary to iodine ingestion in the mothers. Very recently there has been a lot of interest in this in Belgium and Western Europe where Betadyne is a frequently used preparation during deliveries. In Europe, during the last trimester, for reasons which completely escape me, a lot of women douche with Betadyne during the last trimester. There is evidence that some of these newborns, especially the ones that are premature, do go through a period of transient hypothyroidism. In Belgium now, I believe iodine has been banned from use in pregnant women and at the time of delivery. So they are switching to noniodine containing disinfectants.

Deykin (Boston): Lew that was a beautiful presentation. I would like to try to link the last two presentations. PTU has been recommended in some studies as a treatment for delaying the conversion of alcoholic hepatitis to cirrhosis or preventing the fibrosis that is associated with cirrhosis. Do you think that is related in some way to a specific effect of PTU or does it require the inducement of hypothyroidism, and do you think that in any way is stimulated by iodine?

Braverman: There have been some studies from Canada. I believe about five years ago there was a paper in the New England Journal describing the use of propylthiouracil in the prevention of alcoholic cirrhosis. There have been some more recent studies which tend to agree with it, except that the studies have some major problems. None of these patients, as far as I could tell, were made hypothyroid by the administration of propylthiouracil. There is some evidence that the drug does affect oxidative metabolism in hepatocytes. There may be some possible nonthyroid effect of the drug at the level of the liver, but I remain a bit skeptical.

Warthin (Boston): A small historical note. I, and my four siblings, who grew up in Michigan in the teens had small goiters by the time of 1920 when iodine became available in the salt. My father, who was a Pathologist at the University of Michigan Hospital, adamantly refused my mother's use of any iodine-containing medication for a cough or whatnot, because of his fear of our developing Jodbasedow disease. He had trained in Germany in the 1890's and apparently had seen a good deal of it there.

Braverman: That's fascinating because Hart described, I believe in the 1920's, the first outbreak of Jodbasedow disease in this country, but that was in the Great Lakes area where they supplemented iodine by giving the school children and adults drops of Lugols solution every day. The first description of Jodbasedow was in the 1840's in Europe, but again it is basically a European disease, and a disease which occurred in this country when iodine was used as a prophylaxis in the early days for the prevention of iodine deficiency goiter. We see it primarily probably because of our interest in iodine and the fact that nontoxic nodular goiter is very common in the elderly population.