Iodide

Iodide is the oldest remedy for disorders of the thyroid gland. Before the antithyroid drugs were used, it was the only substance available for control of the signs and symptoms of hyperthyroidism. Its use in this way is indeed paradoxical, and the explanation for this paradox is still incomplete.

Mechanism of Action. High concentrations of iodide appear to influence almost all important aspects of iodine metabolism by the thyroid gland (*see* Ingbar, 1972). The capacity of iodide to limit its own transport has been mentioned above. Acute inhibition of the synthesis of iodotyrosines and iodothyronines by iodide also is well known (the *Wolff-Chaikoff effect*). This transient, 2-day inhibition is observed only above critical concentrations of intracellular rather than extracellular concentration of iodide. With time there is "escape" from this inhibition that is associated with an adaptive decrease in iodide transport and a lowered intracellular iodide concentration (Braverman and Ingbar, 1963). The mechanism of the Wolff-Chaikoff effect may involve inhibition of inositol phosphate signaling pathways within the thyrocyte (Corvilain *et al.*, 1994).

A very important clinical effect of high plasma iodide concentration is an inhibition of the release of thyroid hormone. This action is rapid and efficacious in severe thyrotoxicosis. The effect is exerted directly on the thyroid gland, and it can be demonstrated in the euthyroid subject and experimental animals as well as in the hyperthyroid patient. Recent studies in a cultured thyroid cell line suggest that some of the inhibitory effects of iodide on thyrocyte proliferation may be mediated by actions of iodide on crucial regulatory points in the cell cycle (Smerdely *et al.*, 1993).

In euthyroid individuals, the administration of doses of iodide from 1.5 to 150 mg daily results in small decreases in plasma thyroxine and triiodothyronine concentrations and small compensatory increases in serum TSH values, with all values remaining in the normal range. However, euthyroid patients with a history of a wide variety of underlying thyroid disorders may develop iodine-induced hypothyroidism when exposed to large amounts of iodine present in many commonly prescribed drugs (Table 56–6), and these patients do not escape from the acute Wolff-Chaikoff effect (Braverman, 1994). Among the disorders that predispose patients to iodine-induced hypothyroidism are: treated Graves' disease, Hashimoto's thyroiditis, postpartum lymphocytic thyroiditis, subacute painful thyroiditis, and lobectomy for benign nodules. The most commonly prescribed iodine-containing drugs are certain expectorants, topical antiseptics, and radiology contrast agents.

Response to Iodide in Hyperthyroidism. The response to iodides in patients with hyperthyroidism is often striking and rapid. The effect is usually discernible within 24 hours, and the basal metabolic rate may fall at a rate comparable to that following thyroidectomy. This provides evidence that the release of hormone into the circulation is rapidly blocked. Furthermore, thyroid hormone synthesis also may be decreased. The maximal effect is attained after 10 to 15 days of continuous therapy, when the signs and symptoms of hyperthyroidism may have greatly improved.

The changes in the thyroid gland have been studied in detail; vascularity is reduced, the gland becomes much firmer, the cells become smaller, colloid reaccumulates in the follicles, and the quantity of bound iodine increases. The changes are those that would be expected if the excessive stimulus to the gland had somehow been removed or antagonized.

Unfortunately, iodide therapy usually does not completely control the manifestations of hyperthyroidism, and after a variable period of time, the beneficial effect disappears. With continued treatment, the hyperthyroidism may return in its initial intensity or may become even more severe than it was at first. It is for this reason that, when iodide was the only agent available for the treatment of hyperthyroidism, it use was usually restricted to preparation of the patient for thyroidectomy.

Therapeutic Uses. The uses of iodide in the treatment of hyperthyroidism are in the preoperative period in preparation for thyroidectomy and, in conjunction with antithyroid drugs and propranolol, in the treatment of thyrotoxic crisis. Prior to surgery, iodide is sometimes employed alone, but more frequently it is used after the hyperthyroidism has been controlled by an antithyroid drug. It is then given during the 7 to 10 days immediately preceding the operation. Optimal control of hyperthyroidism is achieved if antithyroid drugs are first given alone. If iodine also is given from the beginning, variable responses are observed; sometimes the effect of iodide predominates, storage of hormone is promoted, and prolonged antithyroid treatment is required before the hyperthyroidism is controlled. These clinical observations may be explained by the ability of iodide to prevent the inactivation of thyroid peroxidase by antithyroid drugs (Taurog, 1991).

Another use of iodine is to protect the thyroid from radioactive iodine fallout following a nuclear accident. Because the uptake of radioactive iodine is inversely proportional to the serum concentration of stable iodine, the administration of 30 to 100 mg of iodide daily will markedly decrease the thyroid uptake of radioisotopes of iodine. Following the Chernobyl nuclear reactor accident in 1986, approximately 10 million children and adults in Poland were given stable iodide to block the thyroid exposure to radioactive iodine from the atmosphere and from dairy products from cows that ate contaminated grass (Naumann and Wolf, 1993).

The dosage or form in which iodide is administered bears little relationship to the response achieved in hyperthyroidism, provided not less than the minimal effective amount is given; this dosage is

Table 56–6
Commonly Used Iodine-Containing Drugs

DRUGS	IODINE CONTENT
Oral or local	
Amiodarone	75 mg/tablet
Calcium iodide (*e.g.*, CALCIDRINE SYRUP)	26 mg/ml
Iodoquinol (diiodohydroxyquin)	134–416 mg/tablet
Echothiophate iodide ophthalmic solution	5–41 μg/drop
Hydriodic acid syrup	13–15 mg/ml
Iodochlohydroxyquin	104 mg/tablet
Iodine-containing vitamins	0.15 mg/tablet
Iodinated glycerol	15 mg/tablet
Idoxuridine ophthalmic solution	18 μg/drop
Kelp	0.15 mg/tablet
Potassium iodide (*e.g.*, QUADRINAL)	145 mg/tablet
Lugol's solution	6.3 mg/drop
Niacinamide hydroiodide + potassium iodide (*e.g.*, IODO-NIACIN)	115 mg/tablet
PONARIS nasal emollient	5 mg/0.8 ml
Saturated solution of potassium iodide	38 mg/drop
Parenteral preparations	
Sodium iodide, 10% solution	85 mg/ml
Topical antiseptics	
Iodoquinol (diiodohydroxyquin) cream	6 mg/g
Iodine tincture	40 mg/ml
Iodochlorhydroxyquin cream	12 mg/g
Iodoform gauze	4.8 mg/100 mg gauze
Povidone iodine	10 mg/ml
Radiology contrast agents	
Diatrizoate meglumine sodium	370 mg/ml
Propyliodone	340 mg/ml
Iopanoic acid	333 mg/tablet
Ipodate	308 mg/capsule
Iothalamate	480 mg/ml
Metrizamide	483 mg/ml before dilution
Iohexol	463 mg/ml

SOURCE: Adapted from Braverman, 1994.

5 mg per day in most, but not all, patients. *Strong iodine solution* (Lugol's solution) is widely used and consists of 5% iodine and 10% potassium iodide, which yields a dose of 6.3 mg of iodine per drop. The iodine is reduced to iodide in the intestine before absorption. Saturated solution of potassium iodide also is available, containing 38 mg per drop. Typical doses include 3 to 5 drops of Lugol's solution or 1 to 3 drops of saturated solution of potassium iodide 3 times a day. These doses have been determined empirically and are far in excess of that needed.

Untoward Reactions. Occasional individuals show marked sensitivity to iodide or to organic preparations that contain iodine when they are administered intravenously. The onset of an acute reaction may occur immediately or several hours after administration. Angioedema is the outstanding symptom, and swelling of the larynx may lead to suffocation. Multiple cutaneous hemorrhages may be present. Also, manifestations of the serum-sickness type of hypersensitivity, such as fever, arthralgia, lymph node enlargement, and eosinophilia, may appear. Thrombotic thrombocytopenic purpura and fatal periarteritis nodosa attributed to hypersensitivity to iodide have also been described.

The severity of symptoms of chronic intoxication with iodide (*iodism*) is related to the dose. The symptoms start with an unpleasant brassy taste and burning in the mouth and throat, as well as soreness of the teeth and gums. Increased salivation is noted. Coryza, sneezing, and irritation of the eyes with swelling of the eyelids are

commonly observed. Mild iodism simulates a "head cold." The patient often complains of a severe headache that originates in the frontal sinuses. Irritation of the mucous glands of the respiratory tract causes a productive cough. Excess transudation into the bronchial tree may lead to pulmonary edema. In addition, the parotid and submaxillary glands may become enlarged and tender, and the syndrome may be mistaken for mumps parotitis. There also may be inflammation of the pharynx, larynx, and tonsils. Skin lesions are common, and vary in type and intensity. They usually are mildly acneform and distributed in the seborrheic areas. Rarely, severe and sometimes fatal eruptions (ioderma) may occur after the prolonged use of iodides. The lesions are bizarre, resemble those caused by bromism, a rare problem, and, as a rule, involute quickly when iodide is withdrawn. Symptoms of gastric irritation are common; and diarrhea, which is sometimes bloody, may occur. Fever is occasionally observed, and anorexia and depression may be present. The mechanisms involved in the production of these derangements remain unknown.

Fortunately, the symptoms of iodism disappear spontaneously within a few days after stopping the administration of iodide. The renal excretion of I^- can be increased by procedures that promote Cl^- excretion (*e.g.*, osmotic diuresis, chloruretic diuretics, and salt loading). These procedures may be useful when the symptoms of iodism are severe.

Radioactive Iodine

Chemical and Physical Properties. Although iodine has several radioactive isotopes, greatest use has been made of ^{131}I. It has a half-life of 8 days, and, therefore, over 99% of its radiation is expended within 56 days. Its radioactive emissions include both γ rays and β particles. The short-lived radionuclide of iodine, ^{123}I, is primarily a γ-emitter with a half-life of only 13 hours. This permits a relatively brief exposure to radiation during thyroid scans.

Effects on the Thyroid Gland. The chemical behavior of the radioactive isotopes of iodine is identical to that of the stable isotope, ^{127}I. ^{131}I is rapidly and efficiently trapped by the thyroid, incorporated into the iodoamino acids, and deposited in the colloid of the follicles, from which it is slowly liberated. Thus, the destructive β particles originate within the follicle and act almost exclusively upon the parenchymal cells of the thyroid with little or no damage to surrounding tissue. The γ radiation passes through the tissue and can be quantified by external detection. The effects of the radiation depend upon the dosage. When small tracer doses of ^{131}I are administered, thyroid function is not disturbed. However, when large amounts of radioactive iodine gain access to the gland, the characteristic cytotoxic actions of ionizing radiation are observed. Pyknosis and necrosis of the follicular cells are followed by disappearance of colloid and fibrosis of the gland. With properly selected doses of ^{131}I, it is possible to destroy the thyroid gland completely without detectable injury to adjacent tissues. After smaller doses, some of the follicles, usually in the periphery of the gland, retain their function.

Therapeutic Uses. *Sodium iodide I 131* (IODOTOPE THERAPEUTIC) is available as a solution or in capsules containing essentially carrier-free ^{131}I suitable for oral administration. *Sodium iodide I 123* is available for scanning procedures. Radioactive iodine finds its widest use in the treatment of hyperthyroidism and in the diagnosis of disorders of thyroid function. Discussion will be limited to the uses of ^{131}I.

Hyperthyroidism. Radioactive iodine is highly useful in the treatment of hyperthyroidism, and in many circumstances it is regarded as the therapeutic procedure of choice for this condition (Soloman *et al.*, 1990; for review, *see* Farrar and Toff, 1991). The use of iodide as treatment for hyperthyroidism, however, may preclude, for months, treatment and certain imaging studies with radioactive iodine.

Dosage and Technique. ^{131}I is administered orally, and the effective dose differs for individual patients. It depends primarily upon the size of the thyroid, the iodine uptake of the gland, and the rate of release of radioactive iodine from the gland subsequent to its deposition in the colloid. To determine these variables insofar as possible, many investigators administer a tracer dose of ^{131}I and calculate the ^{131}I accumulated by the gland and the rate of loss therefrom. The weight of the gland is estimated by palpation. From these data, the dose of isotope necessary to provide from 7000 to 10,000 rad per gram of thyroid tissue is determined. Even when dosage is controlled in this manner, it is difficult to predict the response of an individual to a given amount of the isotope. For these reasons, the optimal dose of ^{131}I, expressed in terms of microcuries taken up per gram of thyroid tissue, varies in different laboratories from 80 to 150 μCi. The usual total dose is 4 to 15 mCi. Lower-dosage ^{131}I therapy (80 μCi/g thyroid) has been advocated to reduce the incidence of subsequent hypothyroidism. While the incidence of hypothyroidism in the early years after such therapy is lower, many patients with late hypothyroidism may go undetected, and the ultimate incidence of hypothyroidism is probably no less than with the larger doses (Glennon *et al.*, 1972). In addition, relapse of the hyperthyroid state, or initial failure to alleviate the hyperthyroid state, is increased in patients receiving lower doses of ^{131}I.

Course of Disease. The course of hyperthyroidism in a patient who has received an optimal dose of ^{131}I is characterized by progressive recovery. It is very unusual for any tenderness to be noted in the thyroid region, and most observers have failed to detect any exacerbation of hyperthyroidism from loss of hormone from the damaged gland in patients whose preformed hormone stores have been depleted by antithyroid drug therapy. Beginning a few weeks after treatment, the symptoms of hyperthyroidism gradually abate over a period of 2 to 3 months. If therapy has been inadequate, the necessity for further treatment is apparent within 6 to 12 months.

Depending to some extent upon the dosage schedule adopted, one-half to two-thirds of patients are cured by a single dose, one-third to one-fifth require two doses, and the remainder require three or more doses before the disorder is controlled. Patients treated with larger doses of ^{131}I almost always develop hypothyroidism within a few months.