CASE REPORTS

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Iatrogenic Hypothyroidism From Topical Iodine-Containing Medications

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DEVELOPMENT OF HYPOTHYROIDISM with and without goiter is known to occur in certain persons following prolonged administration of excess iodine.[1-3] Such inhibition of thyroid hormone synthesis has generally been reported following ingestion of excess iodine in the form of iodide. However, organic compounds containing iodine, particularly in a labile form, are also capable of producing this effect.[4] We report here an instance in which two topical iodine-containing medications, iodoform and povidone-iodine, used to cleanse an open wound for almost two years, led to the development of hypothyroidism with a slight goiter. To our knowledge this is the first time iodine in noningested, noninjected form has been implicated in the induction of hypothyroidism.

Report of a Case

In a 26-year-old woman subtotal colectomy with ileostomy was carried out in 1972 and proctosigmoidectomy was done in 1973 because of ulcerative colitis with large pseudopolyps. During the second operation some remaining colonic tissue was found adhered to the vagina. Detachment of this tissue resulted in a small vaginal hole which connected through a lateral tract to a fistular tract existing where the rectum had been. In this situation serous-sanguinous drainage and menses had two exits.

Because the fistula did not close and the vagina did not heal, we undertook corrective surgical operation in 1974. A large abscess was discovered at the top of the fistular tract and was drained; the vaginal defect was also closed, but this repair failed. Following this operation, the perineal fistula was packed three times a week with a plain nonadhering strip (Adaptic, Johnson & Johnson) to prevent closure from the outside before the tract could fill in. Within several months the fistula greatly decreased in size, becoming about 10 cm long and 1 cm in diameter, with the connection to the vagina being about 0.5 cm in diameter and approximately 6 cm from the outside of the body.

In 1975, in an attempt to keep the fistula cleaner and thereby to accelerate healing, we changed our method of packing the tract. Three times a week we swabbed it out with povidone-iodine* (Betadine Surgical Scrub,† The Purdue Frederick Company), followed by packing with a short strip (25 to 30 cm) of 1.3-cm iodoform-impregnated packing (Nu Gauze, Johnson & Johnson).

After about 22 months of this regimen there developed in the patient (now 31 years old) distinct clinical signs of hypothyroidism, which was clearly shown in June 1977 by laboratory measurement of serum T_4 (thyroxine) levels: 2.3 μg per dl (normal, 4.5 to 13.0 μg per dl). A serum sample coincidentally available from February 1977 still contained normal amounts of T_4 (8.1 μg per dl). At the time the diagnosis of hypothyroidism was made, the patient's thyroid was firm and diffusely enlarged to roughly 2½ times normal size. A thyroid-stimulating hormone (TSH)

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*Povidone-iodine = polyvinylpyrrolidone-iodine = PVP-I.

†Betadine Surgical Scrub was used, unknowingly, although Betadine Solution, free of detergents, should be used for wound care.

TABLE 1.—*Iodine Exposure: Sources and Amounts*

Substance	Amount (Percent) and Form of Iodine Present*	Iodine Exposure: Amount of Substance Used (mg)	Iodine Exposure: Amount of Iodine (mg)	Iodine Exposure: Multiple of Recommended Daily Dose†
Table salt	0.01, KI	4,000	0.3	1.5
Povidone-iodine	0.75, available I	200‡	1.5	7.5
Iodoform packing	5.0, CHI_3	400§	20.0	100.0
TOTAL	....	....	21.8	109.0

*The entries for povidone-iodine and iodoform packing are based on personal communications from N. Healy, The Purdue Frederick Company, and H. L. Dickstein, Johnson & Johnson, respectively.

†A value of 0.2 mg was used as the recommended daily dose.

‡It was estimated that 0.2 ml remained within the body after swabbing out the tract.

§Determined by weighing a typical packing strip.

level of 64 μU per ml (normal, less than 10 μU per ml) confirmed primary hypothyroidism.

The patient was immediately placed on a regimen of thyroxine (50 μg per day, increasing gradually over one month to 150 μg per day) to ameliorate the clinical symptoms quickly. Simultaneously we discontinued application of both iodine-containing medications. The perineal fistula was subsequently managed with plain packing and later also with water jet lavage.[5]

We initially entertained a diagnosis of Hashimoto thyroiditis, especially in view of the patient's history of ulcerative colitis, an autoimmune disorder. However, two observations ruled out this possibility: the absence of abnormal levels of both antithyroglobulin and antimicrosomal antibodies and the disappearance of the patient's goiter within only one month after thyroxine therapy was begun.

We calculated the patient's exposure to iodine from all sources as shown in Table 1. It was found that three days per week the patient was exposed to almost 22 mg, or more than 100 times the recommended daily dose, and that 90 percent of this iodine came from the iodoform packing strip. Iodine can be absorbed systemically from povidone-iodine used in surgical practice,[6-8] and it is most probable that the iodine from iodoform is similarly absorbed. We believe the patient actually absorbed a significant amount of iodine through this wound because the strip, when removed, appeared by color and smell to be relatively free of iodine and because drainage from the fistula was minimal. Conservatively we estimate that, apportioned on a daily basis, the patient absorbed 4 mg of iodine out of a theoretical maximum of 9 to 10 mg per day. Lesser amounts have had an inhibitory effect on organic binding of iodine in persons with a history of iodide goiter and hypothyroidism.[9]

Since transient, reversible hypothyroidism due to excess iodine now seemed a good possibility, we completely stopped thyroxine therapy nine months later. The patient remained clinically and chemically euthyroid. Six weeks after cessation of medication the T_4 level was 8.7 μg per dl and the TSH level was 2.6 IU per ml (normal, 1.9 to 5.4 IU per ml). The patient's thyroid, which had been very small during thyroxine suppressive therapy, regained its normal size and remained soft.

Exposure to any chemical agent besides iodine could be readily ruled out as a cause of the hypothyroidism in this case. Acute (subacute) nonsuppurative thyroiditis was another possibility considered to explain the transient nature of the thyroid dysfunction, but since the pattern of clinical symptoms was inconsistent with that characteristic of such thyroiditis, we think this possibility unlikely.

During preparation of this report we measured the inorganic iodide present in the February 1977 serum sample (the only material still available) in an attempt to show absorption of excess iodine directly.*

The inorganic iodide level was 3.0 μg per dl (normal, not more than 1.0 μg per dl in the absence of excess dietary iodine consumption; frequently in the range of 0.2 to 0.5 μg per dl). The protein-bound iodine (PBI) level was 4.5 μg per dl (normal, 4.0 to 8.0 μg per dl), yielding a total serum iodine level of 7.5 μg per dl. However, by the time this analysis was done, the serum sample had been stored for 20 months at −16°C and had undergone four deliberate freeze-thaw cycles. In that time and under such conditions some decomposition of the PBI is expected to have occurred, with a consequent increase in the level of inorganic iodide. We suspect, therefore, that this serum sample, when fresh, contained less than 3.0 μg of inorganic iodide per dl. Though there is no way of knowing with certainty how much of the initial PBI was assayed as inorganic iodide, we estimate on the basis of the T_4 level of this sample (8.1 μg per dl) that the PBI should have been about 5.3 μg per dl rather than 4.5 μg per

*R. L. Gambardella, T. S. LaGanga, J. C. Sparks, and I. P. Sugar of Bio-Science Laboratories provided information and advice concerning analysis of the 20-month-old serum sample for inorganic iodide and protein-bound iodine.

dl. This adjusted PBI value would lead to an inorganic iodide level of 2.2 μg per dl, still clearly above normal. Conversely, adsorption of iodine to the walls of the storage vessel over time could have led to a decrease in the measured values of inorganic iodide and PBI.

The results of the analysis of the February 1977 serum sample, consequently, were consistent with the clinical evidence indicating that excess iodine was absorbed systemically.

Discussion

Many patients have taken large amounts of iodide, often more than 100 mg per day,[10] for respiratory ailments for long periods without adverse effect on the thyroid.[1-3] However, a few persons fail to adapt to high levels of iodine. Though the frequency of occurrence of this effect in the population is very low, enough cases of iodide goiter and hypothyroidism have by now been reported for this phenomenon to be generally known.[1,2,9] In a person predisposed to iodine-induced goiter and hypothyroidism some abnormality of the thyroid probably exists which prevents the usual adaptation to high iodine levels,[1,2] but this abnormality need never manifest itself in any thyroid dysfunction throughout the person's lifetime unless he happens coincidentally to be exposed over a prolonged period to excess doses of iodine.

Here we have reported the development of hypothyroidism with diffuse goiter in a patient exposed to excess amounts of iodine (about 4 mg per day) from iodoform and povidone-iodine used topically for about two years. That iodine in topical form has not been reported previously as a cause of hypothyroidism or goiter is undoubtedly due to the simultaneous occurrence of two rare events: susceptibility to inhibition of thyroid hormone synthesis by excess iodine and prolonged treatment of an open wound with iodine containing medications.

Povidone-iodine, however, has already been reported to induce the Wolff-Chaikoff effect, which involves transient inhibition of thyroid hormone synthesis by excess iodine.[11] Iodide goiter and hypothyroidism are actually the result of the failure to escape from the Wolff-Chaikoff effect in the continued presence of high iodine levels.[1] Therefore, any substance capable of inducing the Wolff-Chaikoff effect has the potential to cause goiter and hypothyroidism in some persons.

In view of the observations described here and in view of the increasing popularity of iodine-containing antiseptics, we urge physicans using any iodine therapy for a long time, even locally on wounds, to be alert to any change in function or appearance of the patient's thyroid gland. Furthermore, we caution against uncritical acceptance of a diagnosis of Hashimoto thyroiditis or idiopathic hypothyroidism without reasonable confirmatory laboratory evidence and without a reasonable search for agents, whether chemical or biological, that may have induced transient, reversible hypothyroidism in a particular person.

Summary

Hypothyroidism developed in a 31-year-old woman following 22 months of treatment of an unhealed perineal fistula with iodoform-impregnated packing strips and povidone-iodine solution. Use of these topical iodine-containing medications was discontinued and the patient placed on a regimen of thyroxine. Nine months later the thyroxine administration was stopped, and the patient promptly regained normal thyroid function. Induction of reversible hypothyroidism under these circumstances could be attributed to prolonged administration of excess iodine, which in rare persons leads to goiter or hypothyroidism, or both. The novel feature of this report is that iodine in topical rather than ingested or injected form was found to be the cause of the thyroid dysfunction.

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