Drug-Induced Thyrotoxicosis: The Surgical Option

Mordechai Lorberboym MD[1] and Pinhas Schachter MD[2]

Departments of Nuclear [1]Medicine and [2]General Surgery, Wolfson Medical Center, Holon, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Abstract

Background: Drug-induced thyrotoxicosis is not uncommon. It may worsen life-threatening arrhythmias and may be refractory to medical treatment. Near-total thyroidectomy presents a valid alternative to medical therapy and should be considered early in the management of the disease.

Objectives: To assess whether near-total thyroidectomy was a viable approach for our patients.

Methods: Twelve patients – 7 men and 5 women, aged 63 to 82 years – presented with drug-induced fulminant thyrotoxicosis following 1 to 12 months of amiodarone treatment (11 patients, mean 7 months) and after a 6 months course of interferon-alpha treatment (one patient). Medical therapy included propylthiouracil in doses up to 1200 mg/day in all patients and a beta-receptor antagonist in seven. Five patients had to stop amiodarone treatment and start high doses of steroids. A thyroid scan was performed in all patients using 5 mCi of Tc-99m pertechnetate. The thyroid scan showed absent uptake of the tracer in the thyroid bed in all patients, precluding the use of radioablation.

Results: Four patients (three with AIT and one with interferon therapy) who did not respond to 3 months of medical therapy required surgical thyroidectomy due to severe unremitting thyrotoxicosis. A near-total thyroidectomy resulted in rapid correction of thyrotoxicosis, enabling continuation of the anti-arrhythmic drug. There were no intraoperative or postoperative arrhythmias. Subsequently, all patients recovered rapidly and remained well and euthyroid on thyroxine replacement therapy.

Conclusions: Since surgery results in rapid control of thyrotoxicosis and permits continued therapy with amiodarone, we suggest that near-total thyroidectomy warrants consideration as a definitive treatment for resistant amiodarone or interferon-induced thyrotoxicosis.

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Amiodarone and, recently, interferon are significant causes of drug-induced thyrotoxicosis. The mechanisms of thyroid damage induced by interferons are usually the type I immune response [1]. Side effects include multiple alterations in thyroid function, such as Graves-like hyperthyroidism and destructive thyrotoxicosis [2-4], some of which are unrelated to autoimmunity [5]. The therapeutic approach in destructive thyrotoxicosis suggests interferon withdrawal and 1–2 months of methylprednisolone treatment; however, thyrotoxicosis may recur later on, when the patient returns to IFNα therapy [2].

Amiodarone is a potent class III anti-arrhythmic drug that also possesses beta-adrenergic blocking properties. It is widely used for the management of various tachyarrhythmias [6] and to a lesser extent for severe congestive heart failure [7]. Amiodarone-induced thyroid dysfunction occurs because of both its high iodine content and the direct toxic effects of the compound on thyroid parenchyma. In contrast to amiodarone-induced hypothyroidism, amiodarone-induced thyrotoxicosis is difficult to treat because differentiating between the two types is tricky. AIT is more common in iodine-deficient regions of the world. Bartalena and associates [8] classified AIT into two subtypes, now termed type 1 and type 2.

AIT is caused by excess iodine-induced thyroid hormone synthesis (type 1 AIT) or amiodarone-related destructive thyroiditis (type 2 AIT), although mixed forms often occur. The clinical presentation of AIT is similar for both types, and the onset is usually rapid and fulminant, particularly in type II AIT. In type I AIT, the simultaneous administration of thionamides and potassium perchlorate is the treatment of choice, while in type II AIT steroids are the most useful therapeutic option. Mixed forms are best treated with a combination of thionamides, potassium perchlorate and glucocorticoids.

However, AIT may be quite resistant to medical therapy alone: the high intrathyroidal iodine content reduces the effectiveness of thionamides and the low suppressed radioactive iodine uptake values make the administration of radioiodine not feasible. Thyroidectomy may therefore represent a valid option for AIT patients resistant to medical treatment.

The anesthetic management of patients suffering from hyperthyroidism should take into consideration the severity of hyperthyroidism and the eventual end-organ injury. While mild hyperthyroidism does not require special anesthetic consideration, severe intraoperative hyperthyroidism is a true emergency and dictates that elective surgeries be delayed. In the case of emergency surgery supportive treatment of the hyperthyroid crisis (storm) includes hydration, cooling, and administration of antithyroid drugs, beta-blockers and sodium iodine [9].

Materials and Methods

Seven men and five women, age 63 to 82 years, were hospitalized with severe drug-induced thyroiditis between 1999 and 2005. One patient developed fulminant thyroiditis following a 6 month course of IFNα treatment for hepatitis C. He developed a rapid tachyarrhythmia with congestive heart failure, delaying the second interferon treatment. Eleven patients received amiodarone therapy

AIT = amiodarone-induced thyrotoxicosis
IFNα = interferon-alpha

for 1–12 months (mean 7 months). The primary manifestations of drug-induced thyrotoxicosis were reoccurrence of atrial fibrillation in five patients; five others had ventricular premature beats and their clinical condition worsened under amiodarone treatment, and one developed severe congestive heart failure. High doses of propylthiouracil up to 1200 mg/day were administered to all patients, a beta-receptor antagonist was added to seven patients, and steroid therapy (60 mg/day prednisone) was started in five patients. Amiodarone treatment had to be stopped in five patients. A thyroid scan was performed routinely in all patients using 5 mCi of Tc-99m pertechnetate to rule out "cold" or "hot" nodules.

Four patients (three with AIT and one on interferon therapy) did not respond to medical treatment after 3 months and required a formal bilateral near-total thyroidectomy due to severe unremitting thyrotoxicosis. Three of the patients were treated with high doses of steroids, one of them with PTU and ipodate without therapeutic effect. One of the patients developed marked impairment of hepatic function in the initial phase of steroid therapy. Therapy was stopped and the patient had severe congestive heart failure due to thyrotoxicosis, with tachycardia of 140–180 that did not respond to medical treatment. Another patient had toxic multinodular goiter treated with methimazole for 20 years. He had a rather large goiter with signs of compression, and thyroidectomy had long been recommended. He began amiodarone treatment for atrial fibrillation and developed thyrotoxicosis after 4 months. The third patient chose surgery over radioiodine ablation. The fourth patient was scheduled for a second course of interferon treatment and was waiting for the thyroiditis to wane. Since ablating the thyroid would have meant postponing the course until a much later date, a multidisciplinary meeting decided for surgical thyroidectomy. Surgery was performed under general anesthesia with alpha and beta-receptor antagonists prepared for use in case of intraoperative thyroid storm.

Results

The thyroid scan showed absent uptake of the tracer in the thyroid bed in all patients, precluding the use of radioablation [Figure 1]. Anesthesia and near-total thyroidectomy were performed without complications despite the presence of severe hyperthyroidism at the time of surgery. Near-total thyroidectomy resulted in rapid correction of thyrotoxicosis. There were no intra- or postoperative arrhythmias. There were no recurrent laryngeal nerve injuries and no hypoparathyroidism in the postoperative period.

The median postoperative hospital stay was 2 days (range 1–4 days). Subsequently, all patients recovered rapidly and remained well and euthyroid on thyroxine replacement therapy after 12 months of follow-up. In all cases thyroid histopathology demonstrated degenerative and destructive follicular lesions with multinuclear cell infiltrate and focal fibrosis. Associated thyroid pathologic conditions included multinodular goiter in one patient.

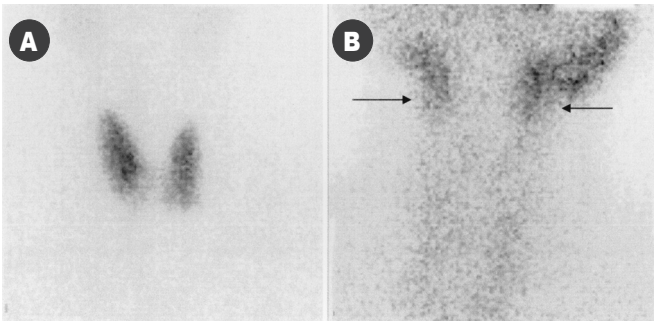

Figure 1. [A] normal thyroid scan compared to **[B]** a scan in a patient with AIT, showing salivary gland activity (arrows) and no uptake of the tracer in the thyroid bed.

Discussion

Amiodarone is a benzofuran derivate with anti-arrhythmic and anti-anginal properties [10]. Each molecule of amiodarone contains two iodine atoms that constitute 37.5% of its mass. A daily dose of the drug results in exposure to a marked iodide excess. Amiodarone has a very long half-life (approximately 100 days), mainly due to its storage in adipose tissue [11]. The use of amiodarone is associated with a wide array of adverse effects. The cornea, lungs, liver, skin and the thyroid are the major organs affected. Thyroid dysfunction was reported in 2–24% of patients treated with amiodarone [12-14]. Hence, the excess iodine is cleared slowly over months and the toxic effects of amiodarone can persist or can even occur well after its discontinuation due to tissue storage of the drug and its metabolites and their slow release [15]. AIT has a relative predominance among men (M:F ratio 3:1) and may develop early or after many years of amiodarone treatment.

The pathogenesis of AIT is complex and not completely understood. Thyrotoxicosis results either from excessive hormone production (type 1) or is due to fulminant destructive thyroiditis and release of large quantities of existing hormone (type 2) [16]. This process is aggravated by the toxic metabolites of amiodarone that inhibit thyroxine breakdown [17]. Type 1 AIT typically occurs in people with preexisting non-toxic multinodular goiter or underlying latent Graves' disease, in whom iodine exposure triggers the development of clinical Graves' disease. This subgroup of AIT patients usually has normal or only slightly elevated serum levels of interleukin-6, while patients with type 2 AIT have higher levels of IL-6, rendering it a good marker of the thyroid-destructive processes [18].

Type 2 AIT is a drug-induced destructive thyroiditis that occurs in individuals with no underlying thyroid disease [19]. In this case the hyperthyroidism is due to release of preformed thyroid hormone from damaged thyroid follicular cells. Mixed forms can occur, in which the different features of type 1 and 2 may coexist, as suggested by the observation that some patients with type 1 AIT may have markedly increased serum IL-6 concentration.

Il-6 = interleukin-6
PTU = propylthiouracil

The clinical presentation of AIT is similar for both types. Onset is usually rapid, although older patients may be asymptomatic or may simply have weight loss or other non-specific symptoms. Sometimes a reoccurrence of atrial fibrillation, as occurred in our patients, suggests the diagnosis. Rarely, type 2 AIT will present with thyroidal pain, fever and other systemic symptoms.

In patients with clear-cut AIT type 1, discontinuation of amiodarone, if possible, is usually recommended. However, if the drug was prescribed for life-threatening ventricular arrhythmias, the benefit of its discontinuation may not be as great as the risk of recurrent arrhythmias. Moreover, even if it is discontinued, the drug remains in the circulation for weeks and even months because of its storage in adipose tissue.

Traditionally, large doses of antithyroid drugs have been used to treat type 1 AIT. However, the frequency of adverse reactions from methimazole and possibly PTU are dose-related. In patients who fail to respond to antithyroid drugs after 2–3 months of treatment, potassium perchlorate has been a useful adjunct [20].

In patients with preexisting thyroid abnormalities the 24 hour thyroid radioactive iodine uptake values are reported in some cases to be normal or increased [21]. However, others have reported low 24 hour uptake values regardless of which type of AIT is present. Most likely, this is due to the high circulating levels of iodine, which blocks uptake of the radioactive tracer used for the test.

In type 2 AIT, steroids are considered the treatment of choice because of their membrane-stabilizing and anti-inflammatory effects. Glucocorticoid therapy should be maintained at relatively high levels for 1–2 months because exacerbations of hyperthyroidism can occur if the drug is tapered too rapidly [22].

Some patients with "mixed" AIT who do not respond to therapy of either antithyroid drugs or glucocorticoids may respond to both agents together. In some persistent cases, neither antithyroid drugs nor glucocorticoids, nor both, have a significant impact on thyroid function even if amiodarone has been discontinued. Discontinuing amiodarone therapy is the main step in the treatment of AIT, but in patients with severe thyrotoxicosis and medical therapy failure surgical thyroidectomy is the only alternative [23,24]. Surgery in patients with severe thyrotoxicosis carries risks of arrhythmias and thyroid storm, although only extremely rare events have been reported.

The mechanisms of thyroid damage induced by type I interferons have not yet been clarified in detail. Type I interferons are currently used for the treatment of chronic viral hepatitis, multiple sclerosis and several hematologic and solid tumors. Side effects include multiple alterations in thyroid function, including Graves-like hyperthyroidism and destructive thyrotoxicosis [4]. Although thyroid dysfunction in patients with interferon treatment may be transient and self-limited, thyroid disorders are not always reversible. The most likely explanation for thyroid disease occurring with type I interferon therapy is an autoimmune reaction or immune system dysregulation. Discontinuation of interferon therapy may be required in patients who develop Graves' disease and overt hyperthyroidism.

Conclusions

Surgery results in rapid control of thyrotoxicosis, is relatively safe and permits continuation of amiodarone therapy. We suggest that near-total thyroidectomy should be considered early in the course of treatment for resistant amiodarone-induced thyrotoxicosis.

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Correspondence: Dr. M. Lorberboym, Dept. of Nuclear Medicine, Wolfson Medical Center, Holon 58100, Israel.
Phone: (972-3) 502-8540
Fax: (972-3) 502-8569
email: mvlorber@zahav.net.il

The fool doth think he is wise, but the wise man knows himself to be fool

William Shakespeare (1564-1616), British playwright and poet

Capsule

Epidermal RANKL controls regulatory T cell numbers via activation of dendritic cells

Regulatory CD4+CD25+ T cells are important in suppressing immune responses. The requirements for the maintenance of peripheral CD4+CD25+ T cells remain incompletely understood. Receptor activator of NF-B (RANK) and its ligand (RANKL; also known as CD254, OPGL and TRANCE) are key regulators of bone remodeling, mammary gland formation, lymph node development and T cell/dendritic cell communication. Loser et al. report that RANKL is expressed in keratinocytes of the inflamed skin. RANKL over-expression in keratinocytes resulted in functional alterations of epidermal dendritic cells and systemic increases of regulatory CD4+CD25+ T cells. Thus, epidermal RANKL expression can change dendritic cell functions to maintain the number of peripheral CD4+CD25+ regulatory T cells. Epidermal RANKL mediated ultraviolet-induced immunosuppression and over-expression of epidermal RANKL suppressed allergic contact hypersensitivity responses and the development of systemic autoimmunity. Therefore, environmental stimuli at the skin can rewire the local and systemic immune system by means of RANKL.

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Eitan Israeli

Capsule

Toxoplasma injectable virulence

Little is known about the molecular determinants of virulence in eukaryotic pathogens like *Toxoplasma gondii* and malaria. Progress has been hampered by inefficient genetic tools, large genomes, and complex life cycles. Using forward genetic analysis, Taylor et al. (*Science* 2006;314:1776) and Saeij et al. (p. 1780) show that a few clustered genes on a single chromosome control the dramatic difference seen in the virulence of natural lineages of the parasite *T. gondii*. The most important of these genes encodes a conserved serine/threonine kinase that is injected into the host cell. Although this process is reminiscent of type III secretion in bacteria, it is mechanistically and evolutionarily distinct.

Eitan Israeli