Approach to the Patient with Amiodarone-Induced Thyrotoxicosis

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Upon completion of this educational activity, participants should be able to

Differentiate the two main forms of AIT

• Choose the more appropriate therapy for either form of AIT

Predict the response to glucocorticoids in patients with type 2 AIT
Select patients who might take advantage from

thyroidectomy

Target Audience

This continuing medical education activity should be of substantial interest to endocrinologists. Disclosure Policy

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Amiodarone, a benzofuranic iodine-rich antiarrhythmic drug, causes thyroid dysfunction in 15-20% of cases. Although amiodarone-induced hypothyroidism poses no particular problem, amiodarone-induced thyrotoxicosis (AIT) is a diagnostic and therapeutic challenge. There are two main forms of AIT: type 1, a form of iodine-induced hyperthyroidism, and type 2, a drug-induced destructive thyroiditis. However, mixed/indefinite forms exist that may be caused by both pathogenic mechanisms. Type 1 AIT usually occurs in abnormal thyroid glands, whereas type 2 AIT develops in apparently normal thyroid glands (or small goiters). Diagnosis of thyrotoxicosis is easy, based on the finding of increased free thyroid hormone concentrations and suppressed TSH levels. Thyroid radioactive iodine (RAI) uptake values are usually very low/suppressed in type 2 AIT, most commonly low or low-normal, but sometimes normal or increased in type 1 AIT despite the iodine load. Color flow Doppler sonography shows absent hypervascularity in type 2 and increased vascularity in type 1 AIT. Mixed/indefinite forms may have features of both AIT types. Thionamides represent the first-line treatment for type 1 AIT, but the iodine-replete gland is not very responsive; potassium perchlorate, by inhibiting thyroid iodine uptake, may increase the response to thionamides. Type 2 AIT is best treated by oral glucocorticoids. The response very much depends on the thyroid volume and the severity of thyrotoxicosis. Mixed/ indefinite forms may require a combination of thionamides, potassium perchlorate, and steroids. RAI is usually not feasible in AIT due to low RAI uptake values. Thyroidectomy represents a valid option in cases resistant to medical therapy. (J Clin Endocrinol Metab 95: 2529-2535, 2010)

The Case

A 66-yr-old man was referred to our Department because of thyrotoxicosis. He had a 2-yr history of paroxysmal atrial fibrillation treated by electroconversion. In the last 6 months, sinus rhythm had been maintained by oral amiodarone (200 mg/d) given in association with antiplatelet therapy. There was no information as to his thyroid function and morphology before the initiation of amiodarone therapy, but he had no history of previous thyroid diseases. In the last 4 wk, he complained of nervousness, palpitations, weight loss (3 kg)

Abbreviations: AIT, Amiodarone-induced thyrotoxicosis; CFDS, color flow Doppler sonography; FT₄, free T₄; MIBI, [^{99m}Tc]2-methoxy-isobutyl-isonitrile; RAI, radioactive iodine; RAIU, RAI uptake.

not associated with changes in appetite, insomnia, and a modest increase in bowel movements.

On physical examination, this patient, whose family history was negative for thyroid disorders, had tachycardic atrial fibrillation (120 beats/min). Blood pressure was 145/55 mm Hg. The thyroid gland was neither increased in volume nor tender, no nodules were palpable, and no bruit was appreciated over the gland. There were no symptoms or signs of Graves' ophthalmopathy.

Serum biochemical tests were as follows: free T₄ (FT₄), 65 pg/ml (84 pmol/liter; normal values, 7.5–15.5 pg/ml); free T₃ (FT₃), 9.8 pg/ml (15.2 pmol/liter; normal values, 3.5–5.7 pg/ml); and TSH, less than 0.01 mU/liter (normal values, 0.4–3.5 mU/liter). Antithyroglobulin, antithyroperoxidase, and anti-TSH receptor antibodies were undetectable. Erythrocyte sedimentation rate, C-reactive protein, and cell blood count were normal. Urinary iodine excretion was markedly increased (9100 μ g/24 h; normal values, 100–300 μ g/24 h). No iodine-containing contrast agents had been recently administered to this patient.

Thyroid ultrasonography evidenced a slightly hypoechogenic gland with an estimated volume of 18 ml and with no nodules; color flow Doppler sonography (CFDS) showed a pattern 0 (absent hypervascularity) and peak systolic velocity measured at the level of inferior thyroid artery was normal (3 cm/sec, normal range 2–7 cm/sec); thyroid radioactive iodine (RAI) uptake (RAIU) was 0.7% after 3 h and 0.9% at 24 h.

Background

The use of amiodarone, a benzofuranic iodine-rich (37% of its weight) antiarrhythmic drug, is complicated in 15–20% of cases by the occurrence of thyroid dysfunction, either thyrotoxicosis [amiodarone-induced thyrotoxicosis

(AIT)] or hypothyroidism (1). The relative proportion of AIT and hypothyroidism partly depends upon environmental iodine intake, because AIT is relatively more frequent in iodine-deficient areas and hypothyroidism in iodine-sufficient areas (2–5). AIT, at variance with spontaneous hyperthyroidism, is more common in men than in women (1).

Two main mechanisms can lead to AIT (Table 1): iodine-induced hyperthyroidism (type 1 AIT), a form of Jod Basedow, or destructive thyroiditis (type 2 AIT), caused by amiodarone itself and its high iodine content (6). However, the two mechanisms may concur to AIT in the same patient (mixed or indefinite AIT) (Table 1). Recent data showed that type 2 AIT is by far the most frequent form (7). This is probably due to the improved pretherapy evaluation of candidates to amiodarone treatment and the avoidance of this drug (if feasible) in patients with preexisting thyroid abnormalities. In fact, type 1 AIT usually occurs in patients with preexisting nodular goiter or latent Graves' disease, whereas type 2 AIT generally develops in patients without clinical, biochemical, and morphological evidence of thyroid disease (1). A small, sometimes moderately painful, goiter may, however, be present also in type 2 AIT (8).

AIT may develop early during amiodarone treatment or even several months after drug withdrawal (1). This is because amiodarone and its metabolites (mainly desethylamiodarone) have a long half-life (up to 100 d) and are stored in various tissues, particularly in the fat, from which they are released very slowly (9, 10). The onset of AIT is often sudden and explosive.

Diagnostic Evaluation

Our patient had relatively few and mild symptoms of thyrotoxicosis associated with the evidence of iodine load

TABLE 1. Clinical and pathogenic features of type 1 and type 2 AIT			
	Туре 1	Type 2	Ref.
Underlying thyroid disease	Yes	No	
Thyroid ultrasound	Diffuse or nodular goiter	Normal (hypoechoic) gland (small goiter)	38
CFDS	Increased vascularity	Absent hypervascularity	13
Thyroidal RAIU	Low/normal/increased	Low/absent	39, 40
MIBI	Thyroid retention	Absent uptake	17
Thyroid antibody	Sometimes present	Usually absent	41–43
Pathogenesis	Iodine-induced hyperthyroidism	Destructive thyroiditis	44, 45
Spontaneous remission	No	Possible	47
Preferred medical therapy	Thionamides (plus KClO4)	Glucocorticoids	6, 31
Subsequent hypothyroidism	Unlikely	Possible	46
Subsequent therapy for the underlying thyroid disease	Likely	No	

Mixed/indefinite forms of AIT are still hypothetical and not yet formally described; their clinical findings are believed to be a mix of amiodaroneinduced destructive thyroiditis and iodine-induced hyperthyroidism. (attributable to chronic amiodarone administration) apparently in the absence of thyroid abnormalities; his main clinical picture was the worsening of cardiac arrhythmia (recurrence of atrial fibrillation) heralded by palpitations. AIT may, however, be heavily symptomatic, especially in younger patients, whose clinical manifestations are indistinguishable from those of spontaneous hyperthyroidism (11, 12).

Identification of the different subtypes of AIT is crucial because this affects the therapeutic approach (Table 1). Thyroid ultrasonography is useful because it shows the presence or absence of a diffuse or a nodular goiter. CFDS of the thyroid is a very important diagnostic tool (13, 14). Type 2 AIT is in most cases characterized by absent hypervascularity (pattern 0), whereas type 1 cases usually show an increased vascularity (patterns 1–3) and blood flow velocity (13–15).

Thyroidal ¹³¹I uptake (RAIU) is another useful diagnostic tool (1). RAIU is usually very low (<3%) in type 2 AIT and low-normal, normal, or even increased (despite the iodine load) in type 1 AIT (8, 15). One study failed to distinguish the two main forms of AIT on the basis of RAIU values (16). The likely explanation is that the presence of diffuse or nodular goiter associated with low thyroidal RAIU does not exclude a destructive or mixed form of AIT.

Recently, thyroid [^{99m}Tc]2-methoxy-isobutyl-isonitrile (MIBI) scintigraphy has been suggested as a useful diagnostic tool in a study of 20 consecutive patients with AIT (17). In this study, MIBI diffuse retention, which is indicative of a hyperfunctioning tissue, was present in all type 1 AIT patients, whereas no significant uptake, suggestive of a destructive process, was found in type 2 AIT; the four patients with mixed/indefinite AIT had either a faint persistent MIBI uptake or a quick washout of the tracer (17). The real usefulness of this expensive procedure in the identification of more complex and more difficult to treat mixed/indefinite forms of AIT needs to be confirmed by larger studies (18).

Other serum biochemical markers, such as IL-6 (usually elevated in type 2 AIT) (1) or C-reactive protein (19), seem to have a marginal diagnostic role in differentiating the different forms of AIT because of their poor specificity (8). Search for thyroid-directed autoantibodies (particularly TSH receptor autoantibody) is relevant only in AIT patients whose underlying and preexisting thyroid disorder is Graves' disease (1).

Thus, although diagnosis of AIT is not difficult *per se*, identification of the pathogenic mechanisms of thyrotoxicosis may be difficult. This is reflected by the results of questionnaire-based surveys in Europe, North America, and Latin America (3–5), with a substantial proportion of respondents unable to distinguish with certainty type 1 and type 2 AIT. However, in general, CDFS and thyroid RAIU determination appear to be the most useful diagnostic techniques in the initial assessment of the patient (Table 1).

Therapeutic Approach

AIT is a dangerous and critical situation for the patient with underlying cardiac abnormalities. Indeed, AIT is bound to an increased mortality, especially in older patients with impaired left ventricular function (20). Thus, restoration and stable maintenance of euthyroidism should be achieved as quickly as possible. On the other hand, the diagnostic uncertainties underscored in the mentioned surveys (3–5) often have an impact on the therapeutic approach; if the physician is unable to define the pathogenic mechanism of AIT, the optimal treatment may not be selected or all possible pharmacological weapons may need to be used at the same time. This, in turn, may imply a higher risk of side effects and complications of therapy.

Type 1 AIT, a form of true hyperthyroidism triggered by the iodine load, is best treated by antithyroid drugs (1). However, an iodine-replete thyroid gland is less responsive to the inhibitory action of thionamides. Thus, higher drug dosages (40-60 mg/d methimazole or equivalent doses of propylthiouracil) and longer periods of therapy are required before euthyroidism is restored. This is obviously not ideal in patients with cardiac problems. To increase the sensitivity of the thyroid gland and the response of thyrotoxicosis to thionamides, potassium perchlorate, which decreases thyroid iodine uptake, is added for 2-6 wk (21). To minimize the adverse effects of the drug (particularly on the kidney and blood marrow), doses of 1 g/d or lower of potassium perchlorate should be used (1). The use of the combined thionamide-potassium perchlorate treatment seems to be more popular in Europe than in North America, where most thyroidologists employ thionamides alone as first-line treatment for type 1 AIT (5).

Type 2 AIT, a form of drug-induced destructive thyroiditis caused by amiodarone itself, is best treated by steroids (5, 6). Type 2 AIT may be self-limiting, and continuation of amiodarone has been suggested by some authors not to influence the effectiveness of steroids (22). Initial prednisone dose is about 0.5-0.7 mg/kg body weight per day, and the treatment is usually continued for 3 months (1). Although the response to treatment often is dramatic, and 50% of patients are cured within 4 wk (23), a delayed response is sometimes observed. However, using a mathematical model, euthyroidism should be reached after 40 d of treatment, unless goiter is large and initial thyrotoxicosis is particularly severe (23). Thionamides are not effective in type 2 AIT. A recent retrospective cohort study showed that after about 6 wk of therapy, more than 85% of patients treated with thionamides were still thyrotoxic compared with 24% of prednisone-treated patients (24).

The most difficult challenge is represented by mixed/ indefinite forms of AIT. In these cases, both pathogenic mechanisms (increased thyroid hormone synthesis and thyroid hormone discharge due to glandular damage) are likely operating. Thus, the best treatment is represented by a combination of thionamides (with or without potassium perchlorate) and oral glucocorticoids (1). However, mixed/indefinite forms of AIT, although proposed as a separate entity, have not been fully characterized so far. The fact that features of hyperthyroidism and destructive thyroiditis may concomitantly be present suggests that destructive phenomena may superimpose to a hyperfunctioning gland. However, how these findings will affect thyroid tests, allowing a clear-cut identification of the underlying process, still is unsettled. If a patient initially treated with thionamides alone (because of a diagnosis of type 1 AIT) does not respond within 4 wk, most thyroidologists usually add potassium perchlorate and/or oral glucocorticoids (3-5). Amiodarone-induced destructive thyroiditis may occur in patients with goiter, making differentiation of type 1 and mixed/indefinite forms very difficult. In these cases, a relevant proportion of thyroidologists (more frequently in North America than in Europe) treat these particular patients with a combination of antithyroid drugs and steroids from the beginning (5). Many thyroidologists think that glucocorticoids may be not easy to handle in patients with cardiac diseases; accordingly, it has been suggested to start medical therapy of type 2 AIT patients with thionamides for at least a month and to associate steroids if response is poor or absent (25). In our opinion, this somehow expectant strategy may be harmful for a patient with (often serious) cardiac abnormalities, whose thyrotoxicosis should be promptly corrected. In addition, no evidence supports such a therapeutic approach.

The use of lithium has been proposed for AIT (26), but the evidence is too limited to support its effectiveness. Iopanoic acid has been initially proposed as a medical therapy for AIT patients (27), but this drug is less effective than glucocorticoids (28). The main advantage of iopanoic acid administration is in the preparation of AIT patients for thyroidectomy, because it rapidly lowers serum T_3 concentrations (29). Plasmapheresis is generally not used because of its transient effects, its costs, and because not widely available (1).

RAI therapy is in principle not feasible in AIT patients because of the low RAIU values either due to the iodine load or the destructive process (1). An open study suggested, however, that RAI may have some value also in these cases (30). Thyroid RAIU values might to some extent be increased by the administration of recombinant human TSH in type 1 AIT, thus allowing RAI therapy (31). This approach may be risky, because recombinant human TSH administration in these patients may be followed by a sustained increase in serum thyroid hormone concentrations (32), which is obviously harmful for patients with underlying cardiac abnormalities.

Total thyroidectomy is not the first-line treatment for AIT, also in view of the potential surgical risk in these patients with underlying cardiac disorders. However, this approach may be necessary in patients who are resistant to other treatments (29, 33, 34). To obtain a better (although transient) control of thyrotoxicosis before surgery, a short course of iopanoic acid (in association with antithyroid drugs) can be used (29); 1 giopanoic acid per day usually normalizes serum T₃ concentrations in 1-3 wk, whereas T₄ remains unchanged. The surgical risk is probably further reduced by a combination of minimally invasive thyroid surgery and local anesthesia (35). We believe that continuing iopanoic acid for 7-10 d after surgery, particularly in patients with very high serum thyroid hormone concentrations before surgery, may be beneficial to avoid serum T₃ surge after iopanoic acid withdrawal. Iopanoic acid has now become unavailable in the market, and scientific authorities and medical societies should consider the possibility to strongly recommend its production for severe cases of AIT.

A therapeutic algorithm of AIT is offered in Fig. 1.

Controversies, Practical Problems, and Unanswered Questions

Several issues remain as to the optimal approach to the patient with AIT.

Should amiodarone be withdrawn once a diagnosis of AIT is made?

The decision of whether amiodarone therapy can be discontinued requires a strict interaction between cardiologists and endocrinologists. In a recent survey among European and North American thyroidologists, amiodarone withdrawal was considered necessary by 90% of Europeans and 79% of North Americans in the case of type 1 AIT; this proportion decreased to 80 and 66%, respectively, in the case of type 2 AIT (5). This question is unsettled, because mild cases of type 2 AIT may remit without treatment and/or amiodarone withdrawal (8). For the time being, we favor amiodarone withdrawal (if feasible from the cardiological point of view), but no controlled



FIG. 1. Proposed algorithm for the management of patients with AIT. Patients with type 1 AIT are preferably treated with methimazole (starting dose, depending on the severity of hyperthyroidism, 40–60 mg/d associated with potassium perchlorate, ≤ 1 g/d). We continue methimazole, at lower doses, until reaching euthyroidism; potassium perchlorate is given for 4–6 wk. Our preferred medical option for patients with type 2 AIT is glucocorticoids, which are given at a starting dose of 0.5–0.7 mg prednisone/kg body weight per day; treatment is usually continued for 3 months; however, in some cases, a longer period of therapy may be necessary. For further details, see text. AMIO, Amiodarone; TX, total thyroidectomy.

and prospective studies so far have addressed this issue. It should, however, be pointed out that the effects of amiodarone on the thyroid may last for several months after amiodarone discontinuation due to its long half-life (1); accordingly, drug withdrawal might not influence the response to medical therapy in the short term. In conclusion, we favor amiodarone withdrawal if it is not risky for the patient from the cardiological standpoint.

What to do once euthyroidism has been restored?

Once euthyroidism has been restored, amiodarone has been withdrawn, and urinary iodine excretion is normal, what should be done for the thyroid? In the above surveys (3–5), thyroid ablation was recommended by three quarters of respondents for the underlying thyroid disorder in type 1 AIT, particularly if thyrotoxicosis recurred; a waitand-see strategy was suggested in the majority of type 2 AIT cases, unless relapse occurred. This is also our approach.

What to do if amiodarone (in the event it has been discontinued) needs to be given again?

This is not an infrequent event. Also, in this case, the suggested approach differs in type 1 and type 2 AIT (3–5). In type 1 AIT, prophylactic thyroid ablation either by RAI therapy or thyroidectomy is recommended by three quarters of thyroidologists, whereas in type 2 AIT, an expect-

ant strategy is applied by more than 60% of respondents (3-5). We agree with the above positions.

What may happen if amiodarone therapy is restarted?

This is an unsettled issue because there are no longitudinal studies addressing this specific issue. Thyrotoxicosis might therefore recur. However, few studies have shown that reexposure to amiodarone or an iodine load may be followed by the occurrence of hypothyroidism (36, 37). In this event, amiodarone needs not to be discontinued, and hypothyroidism is corrected using L-T₄ (1).

Returning to the Patient

The patient had a typical type 2 AIT. His thyroid gland was normal, with absent hypervascularity at CFDS, and thyroid RAIU values were very low. There was no evidence of thyroid autoimmunity. Amiodarone was withdrawn and replaced by β -blocking

agents. He was treated with oral prednisone. The initial dose was 30 mg/d and maintained for 2 wk; the steroid was then gradually tapered and withdrawn after 3 months. Serum free thyroid hormone concentrations normalized after 6 wk and remained normal afterward. His late follow-up visit confirmed a euthyroid state after 2 yr. He had no recurrent paroxysmal atrial fibrillation.

Conclusions

Although the described case was relatively simple and treatment was rapidly successful, AIT remains a diagnostic and therapeutic challenge for the physician. Identification of different subtypes may be difficult and often imprecise. The difficulty in the initial assessment may hamper a correct therapeutic approach. First-line treatment of AIT is generally medical. When a clear-cut diagnosis of type 1 AIT is made, thionamides are the best treatment (possibly associated with potassium perchlorate); if type 2 AIT is diagnosed, steroids are the treatment of choice. However, if a rapid restoration of euthyroidism is necessary and the general conditions of the patient might further deteriorate due to uncontrolled thyrotoxicosis, a short course of iopanoic acid followed by total

thyroidectomy is a valid therapeutic option. RAI has a marginal role in the management of AIT.

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