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Management of amiodarone-induced thyrotoxicosis

Chinnadorai Rajeswaran, Rhidian John Shelton, Stephen George Gilbey

Department of Diabetes and Endocrinology, St. James's University Hospital, Leeds, U.K.

Summary

Amiodarone is used increasingly in a number of cardiac conditions. Amiodarone is heavily iodinated and can cause thyroid dysfunction. The diagnosis of amiodarone-induced thyrotoxicosis remains difficult and more common causes of thyrotoxicosis need to be considered and excluded. Amiodarone has a significant side effect profile, which includes thyroid dysfunction. Amiodarone is an effective drug and its withdrawal may have significant impact on a patient's already fragile cardiac status. There are three different types of amiodarone-induced thyrotoxicosis (AIT) (I, II and mixed). Identification of the different subtypes of AIT allows a rational and appropriate management strategy to be chosen. Type I occurs in patients with underlying thyroid disease, whilst type II is thought to result from a destructive thyroiditis. Differentiation is based on clinical grounds together with investigations, which can include thyroid function test, radioiodine uptake scanning, measurement of interleukin-6 levels and colour flow Doppler sonography. Amiodarone should be discontinued in both types of AIT if the indication for its use is not a life-threatening cardiac condition. The management of type I centres around antithyroid drugs to control thyrotoxicosis and later consideration of more definitive treatment. Type II AIT responds to steroid therapy, although antithyroid drugs may be useful if symptoms are severe. Therapeutic options for refractory cases of AIT include surgery, radioiodine and plasmapheresis.

Key words: amiodarone; thyrotoxicosis; thyroid function test; thionamides; corticosteroids

It is much easier to write upon a disease than upon a remedy. The former is in the hands of nature and a faithful observer, with an eye of tolerable judgement, cannot fail to delineate a likeness. The latter will ever be subject to the whims, the inaccuracies and the blunders of mankind … William Withering, 1785[1].

It is more difficult to write upon an adverse effect of a remedy and much more so on the management of the adverse effect of the remedy.

Introduction

An ageing population with multiple illnesses will increasingly challenge therapeutic skills. Arrhythmia, in particular atrial fibrillation (AF), is one of the commonest clinically significant cardiac conditions. The prevalence of AF is estimated at 0.4% of the general population, increasing with age [2]. It occurs in more than 6% of those over 80 years of age [3]. Amiodarone is a highly effective agent for the prophylaxis and treatment of many cardiac rhythm disturbances [4]. There is an increase in the prevalence of adverse effects due to amiodarone because of its wider use. Side effects of amiodarone include skin photosensitivity, anorexia, nausea, corneal micro-deposits, neurological symptoms (tremors, ataxia, peripheral neuropathy), abnormal liver function test, interstitial pneumonitis, gynaecomastia, cardiac disorders (heart block, sinus bradycardia), epididymitis and thyroid dysfunction [5, 6].

Management of amiodarone-induced thyrotoxicosis (AIT) can be contentious and difficult. In this review article we endeavour to answer the following questions based on the available evidence. (a) Should amiodarone be discontinued in the management of AIT? (b) Should corticosteroids be prescribed for all type II AIT patients, and if so for how long? (c) Are antithyroid medications effective in both types of AIT, and when should antithyroid medications be discontinued? (d) What are the other options available for management of AIT? A brief description of the drug amiodarone, its action on the thyroid gland, the pathophysiology of amiodarone-induced thyroid disorders and relevant investigations is presented before answering the above questions.

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Amiodarone

Amiodarone is an iodinated benzofuran derivative used in the treatment of ventricular arrhythmia, angina, paroxysmal supraventricular arrhythmias and atrial fibrillation (AF) [4]. Randomised trials have also demonstrated the safety of amiodarone in patients with heart failure. US and European cardiology groups recommend that amiodarone be used as a second line anti-arrhythmic drug in patients with paroxysmal AF [7]. Amiodarone is very heavily iodinated and each amiodarone molecule contains 37.2% iodine by mass. Drug doses range from 200 to 600 mg daily. 10% of the drug's iodine content is released daily as free iodide. Amiodarone treatment releases about 7–20 mg of iodide daily, which is about 50–100fold the optimal daily iodine intake [8]. Absorption of oral amiodarone varies greatly between individuals, with a bioavailability of 2–86%. The drug has a significant half-life, as long as 100 days with prolonged use [9]. It bears some homology in structure to the thyroid hormones, which may explain some of its action on the thyroid gland.

Effect of amiodarone on thyroid

Amiodarone contributes to a significant amount of exogenous iodine intake and has complex effects on thyroid metabolism. Long-term amiodarone therapy often results in an altered thyroid function test in euthyroid patients. Dysthyroid states were observed early on (first ten days of treatment) and following intravenous administration [10, 11]. There is no direct relationship between AIT and the daily or cumulative dose of amiodarone [12]; there are however small studies showing the contrary. Amiodarone is known to cause both hypothyroidism and thyrotoxicosis. Hypothyroidism is far more common in iodine-replete areas, and is slightly more frequent in females [10, 13]. Amiodarone induced hypothyroidism (AIH) particularly occurs in patients with underlying Hashimoto's thyroiditis [14, 15]. AIH may develop as early as the second week and has been detected 39 weeks after starting amiodarone [12]. Failure to escape from the Wolff-Chaikoff effect is thought to be the underlying mechanism [15]. Peripheral downregulation of thyroid hormone receptors and competitive inhibition by amiodarone and its metabolite have also been recognised causes for hypothyroidism [16].

AIT has an average reported prevalence of 5% and has a higher prevalence in iodine-deficient areas, especially Europe [17–19]. It is reportedly more common in males [20, 21], possibly reflecting the higher prevalence of cardiovascular disease among men. The usual clinical features of thyrotoxicosis may be blunted by the anti-adrenergic effect of amiodarone, but deterioration in relatively stable cardiac failure or new arrhythmias should prompt further investigation. The typical biochemical findings are undetectable TSH, that is, less than 0.03 mU/L with elevated free T_3 (more than 2.5 nmol/L) and free T_4 (more than 25 pmol/L). A decrease in T_3 and often a marked increase in rT_3 accompany an increased serum T_4 concentration. The mechanism behind this is inhibition of the type I monoiodinase responsible for conversion of T_4 to T_3 and the metabolism of rT_3 to T_2 [22]. Amiodarone does not alter the distribution or fractional removal of T_3 from the plasma pool, but does inhibit thyroid hormone entry into peripheral tissues [23].

In some patients, TSH may be significantly suppressed, with elevated T_4 but normal T_3 values. This may represent subclinical thyrotoxicosis. Other non-specific markers such as ferritin and serum sex hormone binding globulin may be helpful (both may be elevated). Two distinct pathological mechanisms have been described, type I and type II AIT [24, 25]. A mixed variant (type I and type II AIT) is encountered in clinical practice. In mixed type AIT there is probably a degree of destructive thyroiditis and excessive thyroid hormone synthesis secondary to iodine overload.

Type I amiodarone-induced thyrotoxicosis

This mechanism is thought to occur in patients with pre-existing thyroid abnormalities due to excess thyroid hormone synthesis induced by the iodine load. It is suggested that in patients with underlying thyroid problems, such as diffuse or nodular goitre or latent Graves' disease, there is a failure of the gland to react appropriately to the excess iodine load. The iodine triggers increased hormone synthesis in autonomous areas of gland. One study demonstrated an increased uptake of radioactive iodine in AIT patients with pre-existing thyroid disease when compared to AIT controls with no underlying disease [26]. Evidence examining the possibility of an effect on thyroid autoimmunity is conflicting. Several studies looked at the precipitation of *de novo* anti-thyroid antibodies in amiodarone patients. A review concluded that amiodarone was unlikely to precipitate autoimmune antibodies in previously unaffected subjects, but that it may precipitate or exacerbate pre-existing organ-specific autoimmunity in susceptible individuals [23]. There is female preponderance in this type of AIT, perhaps reflecting the increased prevalence of autoimmune thyroid disease among females [27].

Type II amiodarone-induced thyrotoxicosis

This occurs in the apparently normal thyroid, and results from a direct toxic effect of the drug on the thyroid tissue. It is difficult to predict the onset of type II AIT, which may develop at any time during treatment with amiodarone [24]. Amiodarone causes destructive thyroiditis with leakage of stored thyroid hormones into the circulation [20, 26, 28]. Histopathological features include fol-

licular damage and disruption by diffuse fibrosis, epithelial atrophy and lymphocyte infiltration [29–31]. The exact mechanism is not well defined. The cytotoxic effect produced by amiodarone is mainly due to a direct effect of the drug on thyroid cells; in addition, excess iodide may contribute to its toxicity. In this subgroup of AIT patients, where there is destructive thyroiditis, the thyrotoxic phase may be followed by hypothyroidism [27].

Investigations

Differentiation of the two types of thyrotoxicosis described above is the first step in managing the condition effectively [30, 32], although a recent study has suggested that differentiating between the two types of AIT does not influence the management or outcome [33]. Clinical judgement and response to medication often remain the major diagnostic criteria used. Patients may present with overt symptoms of hyperthyroidism including weight loss, decreased appetite, frequent stools, tremor, emotional lability, heat intolerance and oligomenorrhoea. On examination they may have tachycardia, often atrial fibrillation, warm peripheries, fine tremor, thyroid enlargement or nodules, thyroid bruit and myopathy. However, AIT may be complicated by α and β adrenergic blocking properties of amiodarone and its metabolites [34, 35]. Some signs and symptoms may be masked and tiredness and weight loss often predominate.

Thyroid function tests (TFT) remain the mainstay in the diagnosis of AIT. Thyroid stimulating hormone (TSH) level is suppressed, total and free thyroxine levels are elevated, and serum T_3 is raised. Serum reverse T_3 levels would also be high. In some cases TSH may be undetectable or significantly suppressed along with high-normal or raised total T_4 or free T_4, but with T_3 and free T_3 at the lower end of the reference range. This pattern may represent early or subclinical thyrotoxicosis [24]. Serum interleukin 6 (IL-6) is a cytokine that influences B-cell differentiation and T-cell activation. It is synthesised in the thyroid (and other tissues) and is a good marker of the thyroid destructive processes. Serum IL-6 levels have been shown to be normal or mildly raised in type I AIT and markedly elevated in type II [25]. In a trial in 1996 Bartalena et al. concluded that serum IL-6 was helpful in differentiating the two forms of AIT, whereas Eaton et al. in 2002 found it of no value clinically [34, 36]. This discordance may however be explained by iodine intake in the different study areas or unreliability of the commercial assay [37]. Estimating levels of IL-6, however, may not be useful in differentiating other forms of dysthyroid state.

Colour flow doppler sonography (CFDS) is a technique that shows intra-thyroidal blood flow and provides real-time information on thyroid morphology and hyperfunction. CFDS allows quantification of thyroid tissue and assessment of the vascularity of the gland [29, 35]. Type II AIT is associated with absent or grossly reduced vascularity, while type I shows normal or increased blood flow [30]. The use of CFDS has been shown to be effective clinically, and holds promise as a definitive discriminating test [37].

Radioactive iodine uptake is near zero in type II AIT. In type I increased uptake may be seen, but normal or low uptake can also occur [20, 37]. Hence a normal or high uptake effectively excludes type II but a low uptake is of no differential value. In practice low values are common and therefore of little use [37]. In a retrospective study performed to evaluate the usefulness of thallium scintigraphy for visualisation of thyroid morphology and function, a qualitatively reduced uptake by thyroid was seen in euthyroid and hyperthyroid patients treated with amiodarone [38].

The types of AIT, based on the clinical examination, investigations and baseline thyroid condition, are shown in table 1 [25, 37].

Table 1

Types of AIT, based on the clinical examination, investigations and baseline thyroid condition.

	type I AIT		type II AIT
	toxic nodular goitre	Graves' disease	
Baseline thyroid condition	nodular thyroid	"latent" Graves'	normal thyroid
Thyroid exam	nodular thyroid	normal size or diffuse goitre. Bruit may be present	normal size or diffuse goitre
Ultrasound	one or more nodules	diffuse goitre	heterogeneous pattern
CFDS	normal or increased flow	normal or increased flow	decreased flow
Thyroid autoantibodies	absent	present	generally absent
IL-6	normal or high	normal or high	very high
24-hour RAI uptake	low, normal or high	low, normal or high	very low

Management

AIT presents a complex diagnostic and therapeutic challenge. Type I responds to thionamides (methimazole, propylthiouracil) and perchlorates. Thionamides block hormone synthesis by blocking iodine organification and the coupling of iodothyrosines. The effect is delayed because of a large amount of preformed thyroid hormones and may take as long as 2–4 months [26, 32]. The perchlorates competitively block iodide from entering the thyroid by an effect on the Na^+/I^- symporter, thus preventing the further synthesis of thyroid hormone, but have no effect on the iodination process itself [39]. The perchlorate dose has varied between 600–1000 mg/day (16–40 days) and not more, because of serious side effects such as aplastic anaemia [39]. Type II responds to high doses of corticosteroids. Type II AIT is often described as a self-limiting illness [5, 40]; spontaneous remissions of type I AIT have not been documented. Mixed forms of symptomatic AIT, or in which diagnostic tests to differentiate the types of AIT have been inconclusive, are usually treated initially with a combination of steroids, thionamides and potassium perchlorate if warranted [22]. Beta-blockers may be used for symptom control. These could however be altered later on, depending on the response or based on further diagnostic tests which differentiate the two types of AIT [24].

Should amiodarone be discontinued in the management of AIT?

The initial management of amiodarone-induced thyrotoxicosis (AIT) involves the decision whether to discontinue amiodarone or not. The decision would depend on the patients' cardiac condition, the type of AIT and the availability of alternative therapies. Discontinuation of amiodarone alone may not be beneficial in the management of AIT [41], especially those with type I AIT [15]. In fact amiodarone withdrawal may occasionally result in worsening of the symptoms of thyrotoxicosis, as amiodarone is known to have a beta-adrenoreceptor blocking effect and hence masks some of the symptoms of thyrotoxicosis [34, 35]. Amiodarone has a long half-life and its inhibitory action on 5 prime deiodination of thyroxine to triiodothyronine in the peripheral tissues persists for several months following discontinuation of amiodarone [42, 43]. However, withdrawal of amiodarone may be all that is required in the management of type II AIT. In type II AIT most of the patients may become euthyroid in three to five months with discontinuation of amiodarone alone [15]. Recurrences of type II AIT despite being off amiodarone have been documented [37].

There are no randomised control trials to determine the effect of stopping amiodarone in patients with AIT. Current evidence provides mixed results. A retrospective study of 28 patients with AIT (14 type I, 14 type II) examined the effect of either continuing amiodarone or not. The outcome of this study was the same irrespective of whether amiodarone was discontinued or not. In particular, the results showed no significant difference in either the total dose of anti-thyroid drug (carbimazole) to induce euthyroidism, the rate of improvement in thyroid function tests or the rate of relapse of AIT [27].

If amiodarone were prescribed for a non-life-threatening arrhythmia, replacing amiodarone with an alternative form of treatment would be a reasonable option [24]. If however the patient's cardiac condition warrants continuation of amiodarone, then it is always safer to continue with amiodarone and treat the thyrotoxicosis aggressively [24, 44]. Amiodarone withdrawal should be contemplated in symptomatic AIT if there is no detrimental effect on the patient's cardiac status. Can amiodarone be restarted for the management of arrhythmia? If amiodarone must be restarted at a later date, preventive radioiodine treatment is the best option after normalisation of iodide uptake.

Should corticosteroids be prescribed for all type II AIT patients, and if so for how long?

Steroids are effective in type II AIT, and one study showed that steroid treatment alone may be sufficient [45]. Steroids should be used in all patients with type II AIT, with symptoms of thyrotoxicosis and/or worsening arrhythmias [24]. If, however, there are no symptoms of thyrotoxicosis and the patient does not have a life-threatening arrhythmia requiring amiodarone, then the management would initially be amiodarone withdrawal and continued monitoring of thyroid function. Steroids and, later, thionamides could be added if there is any worsening of symptoms of thyrotoxicosis or worsening of arrhythmia requiring recommencement of amiodarone. Prednisolone 40–60 mg daily is used, which may be gradually tapered over a period of three months in the light of the improvement in the clinical and biochemical response [21, 24, 45]. The prednisolone dose is usually decreased when the free thyroxine (T_4) levels are normalised. Biochemical and clinical resolution of the symptoms of thyrotoxicosis may begin as early as the first week of commencing steroids [24, 45]. Prophylaxis for osteoporosis should be considered in patients in whom it is intended to continue steroids for more than three months, and it is advisable to commence bone protective therapy in those with a high risk of osteoporosis. Careful follow-up is a must, as recurrence is common [21, 45]. The limited data available on steroid therapy in type I AIT appear to indicate limited effectiveness [36]. Prednisolone is an anti-inflammatory agent and hence is more effective in type II AIT, where the pathology is predominantly a destructive form of thyroiditis. Nakajima et al.

showed inhibition of amiodarone-induced IL-6 by prednisolone [46]. For a subgroup of patients with a mixed form of AIT, a combination of antithyroid drugs and steroids is probably the most beneficial regimen [47].

Are antithyroid drugs effective in both types of AIT, and when should they be discontinued?

As noted previously, patients with type I AIT rarely respond to withdrawal of amiodarone alone [24]. The management of type I AIT therefore centres on the use of thionamides to block thyroid hormone synthesis. The greatly elevated thyroidal iodine concentration found in patients on amiodarone reduces the effectiveness of these drugs. Higher doses (carbimazole/methimazole 40–60 mg per day or propylthiouracil 100–150 mg qds) are required, which may be reduced after 6–12 weeks [24, 36, 45] depending on the free thyroxine levels. Long-term therapy may be required if amiodarone is continued. Antithyroid drugs may be continued for 3–6 months, and a minority of patients with underlying Graves' disease will remain euthyroid. As most patients with type I AIT have underlying Graves' disease or multinodular goitre, thyrotoxicosis usually recurs and definitive treatment (usually radioiodine) is recommended. In type II AIT, the RAI uptake is low, indicating a very low concentration of iodide organification [15, 24, 47, 48]. Antithyroid drugs alone may be ineffective in type II AIT as there is a low ongoing organification of iodine [5]. There is some evidence to support the use of thionamides in patients with type II AIT in iodine-replete areas. One UK study of 28 cases of AIT (type I and II) found no difference in overall outcome between the two groups when treated with thionamides alone [27]. However, this is in conflict with an Italian study which recommends steroid therapy for AIT type II [36]. This difference was probably due to varying dietary iodine intake between UK and Italian patients.

Thionamides should be commenced for all symptomatic type I and type II AIT patients who do not respond to steroids, and in patients in whom diagnostic tests to differentiate the type of AIT have been inconclusive. Attempts to reduce the dose and discontinue should be based on the clinical symptoms and thyroid function test.

What are the other options available for management of AIT?

Most patients with type I AIT have an underlying thyroid disorder (Graves' disease or multinodular goitre) and recurrence of thyrotoxicosis is therefore common. Radioiodine treatment is usually recommended as a definitive treatment for this form of AIT [24]. The timing and dose of radioiodine treatment will depend on the severity of thyrotoxicosis and the response to antithyroid medications. Radioiodine treatment is not effective in type II AIT.

Amiodarone-associated thyrotoxicosis may be severe and refractory to medical therapy. Despite the potential risks of anaesthesia associated with uncontrolled thyrotoxicosis, thyroidectomy should be considered in the setting of life-threatening thyrotoxicosis [49]. Near total thyroidectomy is ideally a definitive and often preferred treatment option in both forms of thyrotoxicosis, especially when withdrawal of amiodarone is not possible [24, 50, 51–53]. Another treatment paradox is that these patients are at particularly high risk for complications from general anaesthesia. In this subset of patients total thyroidectomy under local anaesthesia may be the best treatment option [54]. Thyroidectomy has been carried out in type I AIT patients, but thyroid surgery in thyrotoxic patients, especially those with underlying cardiac problems, carries a high surgical risk. Thyroidectomy is also an option if amiodarone has to be continued or reintroduced.

A few studies have demonstrated the successful treatment of both type I and type II AIT, with a short course of iopanoic acid (IOP), an oral cholecystographic agent which is rich in iodine [55–57]. Iopanoic acid is a potent inhibitor of 5'-deiodinase, resulting in a marked decrease in the peripheral tissue conversion of T_4 to T_3 [55, 56]. Iopanoic acid has been used to restore euthyroidism prior to thyroidectomy [55]. Plasmapheresis, aimed at removing the excess thyroid hormones from the circulation, has been reported to be efficacious in severe thyrotoxicosis refractory to medical therapy. However, the effect is usually only transient and followed by an exacerbation of AIT [58–60]. Studies using lithium and percutaneous ethanol for the management of AIT have been carried out in the past, but their efficacy and toxicity have not been confirmed in large randomised trials [61, 62].

The management of AIT is a therapeutic challenge, as it follows a heterogeneous course. A flexible therapeutic regime must be adopted on the basis of thyroid status, cardiac condition and the results of the investigations. Until a diagnosis is certain, therapy directed at both types should begin if the patient is symptomatic, including methimazole, prednisolone and, when indicated, perchlorates. The following recommendations can be made: withdraw amiodarone where feasible, treat type I with thionamides, and add perchlorates if the clinical situation warrants. Treat type II AIT with glucocorticosteroids. Mixed AIT should be treated with a combination of thionamides, steroids and perchlorates if warranted. When AIT is refractory to medical treatment, consider surgery. If the patient is rendered euthyroid with medical management, consider RAI as a definitive treatment or for patients requiring amiodarone to be restarted.

Follow-up of patients on amiodarone

Baseline measurements of thyroid function and thyroid antibodies (thyroid peroxide antibody) are essential, as this may reveal individuals who are at risk of developing thyroid dysfunction. The presence of thyroid peroxide antibodies markedly increases the risk of developing AIH. Thyroid function test should be checked every three months for a year and thereafter six-monthly. Frequent measurements of thyroid function test may be required in antibody positive individuals. If TSH remains low (0.03 mU/L–0.3 mU/L) and serum free T_4 and T_3 do not rise above previous values and the patient is clinically euthyroid, no definitive treatment is required but patients would require frequent monitoring of TFT. Type II AIT is difficult to predict and may develop at any time during treatment with amiodarone. There should be a low threshold for performing TFT in patients taking amiodarone. Prolonged monitoring of TFT is required in patients with AIT even if they become euthyroid, as there is a chance of becoming hypothyroid.

Correspondence:
Dr C Rajeswaran
18 Chadwick Crescent
Dewsbury
West Yorkshire
U.K
WF13 2JF
E-Mail: crajesh630@btinternet.com

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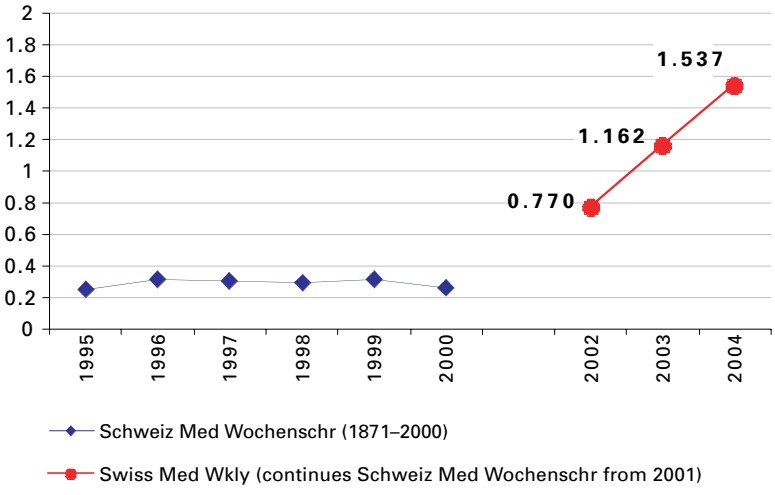

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