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Continuation of Amiodarone Therapy Despite Type II Amiodarone-Induced Thyrotoxicosis

Laurent Uzan,[1] *Laurence Guignat*,[2] *Christophe Meune*,[1] *Stéphane Mouly*,[3] *Simon Weber*,[1] *Xavier Bertagna*,[2] *Jérôme Bertherat*,[2] *Pierre Thomopoulos*[2] and *Denis Duboc*[1]

1 Department of Cardiology, Cochin Hospital, Rene Descartes University, Paris, France
2 Department of Endocrinology, Cochin Hospital, Rene Descartes University, Paris, France
3 Department of Internal Medicine, Lariboisière Hospital, Paris, France

Abstract

Background: Amiodarone is a powerful antiarrhythmic drug; however, its use may be complicated by thyrotoxicosis. When this occurs, clinicians must balance the continuation of amiodarone for antiarrhythmic purposes, and the discontinuation of treatment in order to prevent aggravation of the thyrotoxicosis. We studied the consequences of continuation or cessation of amiodarone in patients with type II amiodarone-induced thyrotoxicosis.

Methods: Consecutive patients who developed type II amiodarone-induced thyrotoxicosis between September 1997 and September 2000 were studied. Amiodarone was continued in patients with previous ventricular arrhythmia or supraventricular arrhythmia associated with severe haemodynamic changes and was withdrawn in the other patients. In patients with persistent, severe symptomatic thyrotoxicosis, corticosteroids were added to therapy.

Results: Thirteen patients were studied (nine with previous atrial fibrillation/flutter and four with ventricular tachycardia). Amiodarone treatment was continued in ten patients, including eight patients who received corticosteroids, and was temporarily halted in three patients. All patients recovered, with no difference in the duration of thyrotoxicosis between the two groups. Corticosteroid treatment was well tolerated and seemed to hasten the return to a euthyroid state (mean of 3.7 ± 0.7 months vs 6.3 ± 1.7 months). No recurrence of hyperthyroidism occurred during long-term follow-up.

Conclusion: In patients who require amiodarone, treatment may be safely continued despite the development of type II amiodarone-induced thyrotoxicosis.

Background

Amiodarone is a powerful antiarrhythmic drug used in the management of supraventricular and ventricular arrhythmias.[1-4] However, the large iodine load associated with its administration often causes thyroid dysfunction, and thyrotoxicosis occurs in 3–12% of treated patients.[5,6] This drug-induced thyrotoxicosis is associated with high morbidity[7] and consists of two types:[5,8] type I thyrotoxicosis occurs in patients with pre-existing thyroid disease, whereas type II, which is by far the most common, is a form of 'destructive thyroiditis' that develops after several months or years of drug exposure in patients with previously normal thyroid glands.[8-10]

Although it sometimes resolves spontaneously,[9,10] amiodarone-induced type II thyrotoxicosis may require treatment with corticosteroids; the efficacy of such treatment, after discontinuation of amiodarone, was established by Bartalena et al.[11] in a series of 12 patients.

In the presence of amiodarone-induced thyrotoxicosis, it has been recommended that amiodarone be withdrawn[8] in order to eliminate the associated iodine overload. However, withdrawal of amiodarone may be seriously detrimental, especially for patients presenting with ventricular arrhythmias or supraventricular arrhythmias coexisting with severe underlying heart disease.

We have reported the consequences of continuing amiodarone treatment despite the development of type II amiodarone-induced thyrotoxicosis.

Material and Methods

Between September 1997 and September 2000, we identified 13 consecutive patients (11 men and two women, aged 58 ± 19 years), who had developed type II amiodarone-induced thyrotoxicosis. They were entered into a prospective database after they had granted their informed consent. The diagnosis of type II amiodarone-induced thyrotoxicosis was based on the following criteria:[8]

- biological tests, including a profoundly decreased thyroid stimulating hormone (TSH) level;
- an absence of previous relevant thyroid disease and the normality of past thyroid tests, together with the absence of anti-thyroid antibodies and goitre, suppressed radioactive tracer uptake during non-contrasted scintigraphy and a normal echogram;
- prolonged treatment with amiodarone together with the absence of any other source of iodine excess.

The cardiovascular diagnosis, indications for treatment with amiodarone, severity of thyroid dysfunction, therapeutic interventions received and follow-up were recorded and reported for each patient. The choice of therapy (i.e. amiodarone continuation or withdrawal) and the decision to employ additional treatment were at the discretion of the practitioner.

The normal ranges for serum TSH, free thyroxine (FT4) and free tri-iodothyronine (FT3) levels are 0.4–4.5mUI/L, 11–23pmol/L, and 3–7pmol/L, respectively (Bayer Advia Centor assays).

The protocol for this study was approved by the appropriate local ethics committee.

Results

Table I outlines the baseline characteristics of the individual patients, whereas table II presents the characteristics of the patients stratified according to whether or not they continued amiodarone treatment. All patients were receiving a daily amiodarone dosage of 200 mg/day and the mean time between initiation of amiodarone treatment and diagnosis of thyrotoxicosis was 35 ± 12 months. The majority of patients had underlying heart disease and, in all patients, antiarrhythmic drugs other than amiodarone and β-adrenoceptor antagonists (β-blockers) were either ineffective or contraindicated.

In the ten patients who had previously experienced either ventricular arrhythmias or supraventricular tachycardia associated with severe haemodynamic changes, amiodarone treatment was continued. Of these, eight patients had highly symptomatic thyrotoxicosis (important weight loss, diarrhoea, palpitations, etc.), together with profoundly decreased TSH levels and elevated FT4 levels. At the discretion of the clinician, amiodarone was continued in combination with prednisone at a dosage of 0.5 mg/kg/day (or 1 mg/kg/day in the absence of a rapid therapeutic response) in these patients, for an average of 14 weeks (table I). In the remaining three patients, amiodarone was temporarily discontinued.

None of the patients were treated with either antithyroid agents or perchlorate.

All patients recovered, including those who did not discontinue amiodarone treatment (table II). In the three patients who discontinued amiodarone, amiodarone was resumed at 5, 8 and 48 months of follow-up, respectively, without subsequent recurrence of thyrotoxicosis.

Corticosteroid treatment appeared to hasten the return to a euthyroid state, as patients who received corticosteroid therapy became euthyroid within a mean of 3.7 ± 0.7 months, compared with 6.3 ± 1.7

Table I. Baseline characteristics of individual patients

Patient number	Age (y), sex	Type of arrhythmia	Type of underlying heart disease	LVEF (%)	TSH level (mU/L)	FT4 level (pmol/L)	FT3 level (pmol/L)	Symptoms of thyrotoxicosis (yes/no)	Duration of thyrotoxicosis (mo)	Prior β-adrenoceptor antagonist use (yes/no)	Corticosteroid treatment (yes/no)
Patients who continued amiodarone treatment											
1	54, m	AF	Valvular disease	30	<0.01	>100	15.0	Yes	5	Yes	Yes
2	72, m	VT	Ischaemic cardiomyopathy	30	<0.01	42.4	5.2	Yes	3	Yes	Yes
3	55, m	VT	Ischaemic disease	65	<0.01	>100	14.2	Yes	3	Yes	Yes
4	72, m	AF	Hypertrophic cardiomyopathy	60	<0.01	>100	11.1	Yes	3	Yes	Yes
5	63, m	AF	Valvular disease	60	<0.05	80	13.9	Yes	4	Yes	Yes
6	53, m	AF	AF associated with repetitive clot migration	60	<0.01	>100	11.6	Yes	4	Yes	Yes
7	57, m	VT	Hypertrophic cardiomyopathy	45	<0.01	41.8	8.4	Yes	4	Yes	Yes
8	70, m	VT	Valvular disease	55	<0.05	33.4	6.6	Yes	7	No	No
9	18, f	AF	Congenital heart defect	NR	0.09	60	11.0	Yes	3	No	Yes
10	70, m	AF	Ischaemic disease	60	0.05	32	NR	No	6	Yes	No
Patients who temporarily discontinued amiodarone treatment											
11	69, m	AF	None	60	0.02	47.2	6	Yes	4	No	No
12	82, f	AF	Valvular disease	60	0.05	61	16.5	Yes	4	Yes	Yes
13	20, m	AF	Duchenne muscular dystrophy	40	<0.01	>100	24.8	Yes	8	No	Yes

AF = atrial fibrillation/atrial flutter; **f** = female; **FT3** = free tri-iodothyronine; **FT4** = free thyroxine; **LVEF** = ejection fraction; **m** = male; **NR** = not reported; **TSH** = thyroid stimulating hormone; **VT** = ventricular tachycardia.

Table II. Characteristics according to amiodarone therapy[a]

Characteristic	Amiodarone therapy	
	uninterrupted	temporarily halted
No. of patients	10	3
Age (y)	58.4 ± 16.2	57.0 ± 32.7
Men/women (no.)	9/1	2/1
Exposure to amiodarone before diagnosis (mo)	33.5 ± 12.4	38.6 ± 8.3
Duration of thyrotoxicosis (mo)	4.2 ± 1.4	5.3 ± 2.3
Duration of euthyroidism following corticosteroid treatment (mo)	33.5 ± 13.1	47.0 ± 25.0

a Unless specified otherwise, values are means ± SD.

months in patients who did not receive such treatment.

Three patients developed transient hypothyroidism that lasted for 4 weeks (all were treated with corticosteroids and continued amiodarone; hypothyroidism occurred after corticosteroid withdrawal).

Following a mean of 41 ± 17 months of follow-up, no patient had presented with recurrent thyrotoxicosis (table I).

Adverse Events

Two patients developed transient corticosteroid-induced diabetes mellitus. Neither thyrotoxicosis nor corticosteroid therapy resulted in unstable cardiovascular function in any patient. One patient (patient nine) died from perioperative cardiac complications during follow-up. The patient was in a euthyroid state at the time of death.

Discussion

The management of cardiac arrhythmias remains a serious clinical problem. Despite the rapidly growing use of cardiac device therapy, antiarrhythmic drugs are still needed in a large number of patients.[1,12] Amiodarone is a class III antiarrhythmic drug that is considered to be the most effective drug for the prevention and treatment of both supraventricular and ventricular arrhythmias, and it is considered to be safe for treatment of these in the presence of severe underlying heart disease.[1-4] In addition, most device-based therapies are used in the prevention of ventricular arrhythmias.

Device-based therapy to prevent atrial fibrillation has been proposed, but this is currently reserved, due to bad tolerance of repetitive shocks, to a very limited number of indications. Radiofrequency ablation is an alternative option that has demonstrated its efficacy,[13] but it is an invasive method and is not routinely performed, particularly in patients with severe underlying cardiac disease (i.e. heart failure or valvular diseases); moreover, supraventricular arrhythmias may be associated with poor haemodynamic conditions in such patients.[14,15] The prevention of supraventricular arrhythmias may be a crucial issue, and amiodarone has been proven to be effective and safe in this setting, and is recommended in these high-risk patients.[4]

Recent reports have highlighted the superiority of cardiac devices over amiodarone therapy for the prevention of ventricular arrhythmias.[16] Nevertheless, amiodarone is often used in association with device-based therapy. In addition, a few case reports have addressed the possibility of 'arrhythmia storms' in patients implanted with cardiac devices. Cardiac devices may protect these patients from sudden death but do so with badly tolerated, repetitive electric shocks, and may not be effective for the prevention of haemodynamic deterioration following repeated ventricular arrhythmias and cardioversion.[17] In a recent study, Credner et al.[18] demonstrated that these repeated arrhythmia storms are associated with an unfavourable prognosis and may be effectively prevented and treated using amiodarone.[18,19]

Thyrotoxicosis during amiodarone treatment is a therapeutic challenge. Withdrawal of the drug is frequently suggested,[8] but may have life-threatening cardiac consequences. In addition, amiodarone and its metabolites remain available in the body for several months following withdrawal of treatment because of their long half-lives (40–60 days).[8] Moreover, the decision to withdraw or continue amiodarone is complicated by the heterogeneous

populations and small numbers of patients that have been included in studies.

Prior to the initiation of amiodarone therapy, an up-to-date assessment of the rhythmic disorder and the patient's condition should be carried out, integrating the existence of new interventional therapeutic modalities and their possible inclusion in the patient's treatment. Following this, to aid in the decision of whether to continue or withdraw amiodarone therapy, distinction between type I and type II amiodarone-induced thyrotoxicosis should be attempted.[8] Type I amiodarone-induced thyrotoxicosis occurs in patients with pre-existing abnormalities of thyroid function (often pretoxic). In these cases, excess iodine induces an abnormal increase of thyroid hormone synthesis and release, and it is logical to withdraw the iodine-containing drug, unless absolutely indicated because of the cardiac condition of the patient. On the other hand, type II thyrotoxicosis develops in patients with normal or, at least, previously non-thyrotoxic thyroid glands and exhibits all features of a destructive thyroiditis:[8] radioactive iodine uptake is low; colour flow Doppler sonography does not show hypervascularity; serum interleukin 6 levels are increased; corticosteroid treatment is effective; and evolution of the condition is, most often, favourable, with recovery in 5–6 months, which may be followed by a transient hypothyroidism. Amiodarone therapy may theoretically be safely continued, as has already been suggested.

In two of the ten patients studied in the first report describing amiodarone-induced thyrotoxicosis in patients with normal thyroid glands (i.e. type II amiodarone-induced thyrotoxicosis),[9] iodine excess was still present after recovery. This persistence of iodine excess was related to amiodarone treatment in the first patient, and to lipiodol myelography in the second.[9] In addition, more recent studies have reported remission of thyrotoxicosis (either spontaneous or during treatment with antithyroid drugs), despite continuation of amiodarone therapy,[6,20-22] although the latter study did not make any distinction between type I- and type II amiodarone-induced thyrotoxicosis. However, in our experience, distinctions are made between the two types of amiodarone-induced thyrotoxicosis on a routine basis, and we report a favourable outcome in patients with type II disease who continued amiodarone therapy. In all the patients included in this study, regardless of their status regarding cessation of amiodarone therapy, euthyroidism was obtained in 3–8 months. The achievement of euthyroidism was followed by transient hypothyroidism in three patients. Moreover, the severe thyrotoxicosis at presentation does not seem to interfere with the achievement a favourable outcome, as several of our patients had severe thyrotoxicosis and an FT4 level of >100 pmol/L (the upper limit of our assay in undiluted plasma) at presentation. Lastly, no patient experienced recurrence of hyperthyroidism during the 41 ± 17 months of follow-up.

Our results, combined with those previously reported, may have important clinical implications as, according to a recent international survey,[23] 80% of physicians discontinue amiodarone therapy in patients with any type of amiodarone-induced thyrotoxicosis. The question of the reintroduction of amiodarone is not addressed in our study, as amiodarone was only discontinued in three patients. In the largest known study of the reintroduction of amiodarone therapy in patients for whom treatment was previously discontinued due to amiodarone-induced thyrotoxicosis, 9% of such patients developed recurrent thyrotoxicosis.[24]

Limitations

Our study is descriptive. Amiodarone continuation or cessation, and corticosteroid use were decided by the practitioner and were not influenced by an established protocol. However, both short- and long-term favourable outcomes in our patients support the option of amiodarone continuation when it is needed for the management of cardiac disease.

Recent guidelines recommend the liberal use of implantable cardioverter defibrillators to prevent sudden death, particularly in patients with depressed left ventricular function. However, antiarrhythmic drugs are still needed in this population to prevent frequent delivery of electric shocks.

Conclusion

The management of amiodarone-induced thyrotoxicosis remains a therapeutic challenge, as it usually develops in patients with pre-existing cardiovascular disease. We report that amiodarone may be

safely continued in patients with type II amiodarone-induced thyrotoxicosis and that corticosteroids may hasten the return to a euthyroid state. The decision to continue amiodarone treatment should, therefore, be based on the need to prevent arrhythmias, the existence of alternative adequate strategies and the severity of the underlying heart disease and contraindications to the use of other antiarrhythmic drugs. Amiodarone therapy should not be automatically interrupted, as has been previously recommended and is the usual practice.

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Correspondence and offprints: Dr *Christophe Meune*, Department of Cardiology, Cochin Hospital, 27 rue du Fg St-Jacques, Paris, 75014, France.
E-mail: christophe.meune@cch.ap-hop-paris.fr