

# Total thyroidectomy for amiodarone-associated thyrotoxicosis: should surgery always be delayed for pre-operative medical preparation?

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## Abstract

**Objective:** Amiodarone can induce severe hyperthyroidism that justifies its withdrawal and the introduction of antithyroid drugs. Continuing amiodarone use, failure to control hyperthyroidism and poor clinical progress may require thyroidectomy. This study aimed to evaluate patients' post-operative development and mid-term outcome after thyroidectomy for amiodarone-associated thyrotoxicosis.

**Study design:** Prospective case series.

**Setting:** Tertiary care centre.

**Subjects and methods:** We prospectively collected cases of amiodarone-associated thyrotoxicosis requiring thyroidectomy due to failure of antithyroid treatment, despite amiodarone discontinuation. Post-thyroidectomy complications were compared immediately, 30 days and one year post-operatively, and also for scheduled versus emergency surgery cases.

**Results:** Of 11 total cases, nine scheduled thyroidectomy cases had no morbidity after elective surgery. Two cases required emergency surgery for multiple organ failure and cardiac problems. Immediate post-operative complications (mostly haemodynamic) occurred in both cases (emergency vs routine surgery,  $p = 0.018$ ).

**Conclusion:** In such cases, pre-operative medical treatment is vital to limit peri- and post-operative complications, but surgery should not be delayed if the haemodynamic status deteriorates. Surgery, with careful anaesthesia, is the cornerstone of the treatment.

**Key words:** Amiodarone; Thyrotoxicosis; Thyroidectomy

## Introduction

Amiodarone is a class III anti-arrhythmic drug and is very effective in the management of supraventricular, junctional and ventricular rhythm disorders. However, hypo- or hyperthyroidism frequently occurs in patients taking this drug.<sup>1–3</sup> Hyperthyroidism is particularly frequent in iodine-deficient regions of Europe, Australia and New Zealand.<sup>4,5</sup> Amiodarone is discontinued in the presence of clinical signs suggestive of thyrotoxicosis, or following the occurrence of cardiothyrotoxicosis (i.e. reappearance of previously controlled rhythm disorders and/or heart failure and/or angina pectoris). The need to continue amiodarone administration due to severe cardiac disorders, and the negative progression of cardiothyrotoxicosis despite well-managed treatment, can lead to thyroidectomy.

Anaesthetising a patient with a delicate haemodynamic status is challenging. On the one hand,

medical pre-operative treatment is mandatory in order to limit peri- and post-operative complications. On the other hand, prolongation of pre-operative medical preparation could delay surgery.

This study aimed to investigate the post-operative progress and mid-term outcome of patients undergoing total thyroidectomy for amiodarone-associated thyrotoxicosis, whether carried out routinely or as an emergency.

## Patients and methods

### Patients

The study was approved by the Hospital Val de Grâce review board.

From 2000 to 2008, we prospectively collected data on cases of amiodarone-associated thyrotoxicosis requiring thyroidectomy. Amiodarone was discontinued in all patients. In most cases, this decision had

been taken months before surgery, following the diagnosis of amiodarone-associated cardiomyopathy. This was related to either clinical signs of thyrotoxicosis or the reappearance of rhythm disorders previously controlled with amiodarone. Surgical treatment was considered because of the failure of medical treatment, with an absence of rapid clinical improvement, no significant decrease in thyroid hormone levels, and severe underlying cardiomyopathy. Thyroidectomy was therefore required in order to achieve a rapid return to a euthyroid state and to enable reintroduction of amiodarone. In all cases, standard total thyroidectomy was performed.

### Method

The data collected included age, underlying cardiomyopathy, free thyroid hormone (T4) level one week before surgery, and medical treatment received. We noted any clinical change before surgery, especially in the period between the discontinuation of amiodarone and the thyroidectomy. We also investigated immediate post-operative complications, and post-thyroidectomy morbidity 30 days and one year after surgery.

### Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences software program for Personal Computer use. Complications after scheduled versus emergency surgery were compared using an unpaired non-parametric test (Mann–Whitney). Differences were considered statistically significant at a *p* value of less than 0.05.

### Results

Eleven cases were reported. Patients' characteristics in the pre-operative period are shown in Table I. Two patients required emergency surgery due to multiple organ failure and cardiac decompensation (patients 10 and 11). Patient age had a mean  $\pm$  standard

deviation (SD) of  $70 \pm 13.5$  years (range, 41–86 years). Ten patients were male and one female (patient 10).

Amiodarone was prescribed for a clearly documented underlying cardiomyopathy (i.e. symptomatic supraventricular rhythm disorders refractory to other therapies).

Following the appearance of thyrotoxicosis, amiodarone was discontinued in all cases, and an antithyroid medical treatment was initiated. All the patients received 60 mg/day carbimazole, which was combined with corticotherapy (methylprednisolone 0.5 to 1 mg/kg/day) in eight patients, and also with potassium perchlorate (600 mg/day) in five of those eight. Medical treatment lasted for a mean  $\pm$  SD duration of  $35.6 \pm 17.7$  days before surgery.

The mean  $\pm$  SD value of the pre-operative free T4 level was  $77.4 \pm 53.3$  pmol/l (normal values, 10–28.20 pmol/l).

Surgery was performed on nine patients under normal operating conditions, after acknowledgement that the medical treatment had failed.

Extreme emergency surgery was required for the two remaining patients. These patients presented with severe cardiomyopathy, and the surgery recommended by the cardiologists was delayed while the anaesthetists attempted to optimise the patients' status. Despite their medical preparation, the peri-operative status of these two patients rapidly declined, with multiple organ failure.

Patient 10 remained on artificial ventilation for 9 days after surgery, which was attributed to pre-operative multiple organ failure. Once thyroidectomy was performed, a loading dose (300 mg) of amiodarone was injected, which resulted in the immediate return of normal sinus rhythm.

Patient 11 suffered from an anaphylactic shock due to the suxamethonium used during induction of anaesthesia. Cardiac arrest resulted. Resuscitation was especially difficult, which could have been related to the patient's poor underlying cardiac status, associated

TABLE I  
PATIENT CHARACTERISTICS

Pt no	Age (y)	Underlying cardiomyopathy	Pre-op FT4* (pmol/l)	Clinical status 1 wk pre-op
1	41	LV arrhythmogenic dysplasia	192	Ventricular tachycardia, cachexia
2	78	CA & AF	31.5	Viral infection, cachexia
3	70	$\uparrow$ BP, CA & AF, ischaemic cardiomyopathy	49.2	Continuous tachyarrhythmia
4	65	$\uparrow$ BP, CA & AF	65.3	AF, change in health status
5	82	CA & AF, ischaemic cardiomyopathy	59.8	AF, change in health status
6	72	CA & AF, $\uparrow$ BP, non-obstructive cardiomyopathy	31.6	AF, VT, cachexia
7	50	CA & AF, congestive cardiomyopathy	145.8	Status epilepticus, cachexia
8	77	CA & AF, ischaemic cardiomyopathy	38.2	Angina, change in health status
9	74	CA & AF, ischaemic cardiomyopathy	110	AF, change in health status
10	86	CA & AF, $\uparrow$ BP, cardiac insufficiency	30.8	Continuous tachyarrhythmia, cachexia & change in health status, then severe renal, hepatic & CV failure
11	76	CA & AF, $\uparrow$ BP	97.3	High output heart failure

\*Normal values were 10–28.20 pmol/l for patients 1 to 9 and 12–22.5 pmol/l for patients 10 and 11. Pt no = patient number; y = years; pre-op = pre-operative; FT4 = thyroxine; wk = week; LV = left ventricular; CA = cardiac arrhythmia; AF = atrial fibrillation;  $\uparrow$ BP = high blood pressure; VT = ventricular tachycardia; CV = cardiovascular

with thyrotoxicosis, despite extended pre-operative medical preparation. This patient remained in intensive care for 10 days.

In contrast to these two cases, there was no specific post-operative morbidity in the cases undergoing routine surgery.

The rate of post-operative complication was significantly higher in the emergency surgery cases than in the routine thyroidectomy cases ( $p = 0.018$ ). There was no mortality, even for the two severe cases, and no hypocalcaemia or hoarseness of voice due to recurrent nerve palsy. At 30 days and at one year post-surgery, no related complications were reported in any of the subjects. Cardiac status was described as stabilised by the referent cardiologists.

## Discussion

In our series, post-operative complications occurred more frequently in thyroidectomy cases which were delayed due to a belief that extended pre-operative medical preparation would optimise the patient's poor haemodynamic state. In fact, patients' cardiac status continued to deteriorate and emergency thyroidectomy was then carried out. Despite the small number of patients included in this study, this result suggests that thyroidectomy should not always be delayed in patients with rapid cardiac deterioration. On the contrary, the surgeon should proceed urgently with thyroidectomy as the cornerstone of treatment.

Amiodarone-associated thyrotoxicosis has a complex pathophysiology that is not fully understood. It can be explained by several mechanisms: the Wolff–Chaikof escape phenomenon induced by elevated levels of circulating iodine; the structural analogy of amiodarone (a benzofuranic derivative rich in iodine) with the thyroid hormones that cause inhibition of 5-monodesiodase (which ensures the peripheral conversion of the inactive prohormone T4 into active tri-iodothyronine); direct cytotoxic effects; and immunomodulatory properties.<sup>2,3</sup> Two main clinical types are described: type I (20 per cent), with hyperfunctioning of a thyroid gland with prior pathology (e.g. multinodular goitre or Grave's disease); and type II (80 per cent), a true iodine-induced thyroiditis with elevation of interleukin 6, which occurs in the absence of a history of thyroid disease.<sup>6,7</sup> However, mixed forms with features of both type I and type II may be quite frequent.

The discontinuation of amiodarone is not always possible, but several alternative drug treatments are available. Carbimazole and propylthiouracil may be used, which inhibit thyroid hormone synthesis for the period required for the clearance of amiodarone and of the elevated levels of circulating iodine. Potassium perchlorate may also be used; this accelerates the elimination of intrathyroid iodine. Finally, corticoids may also be used, enabling rapid restoration of a euthyroid state in patients with poor tolerance of thyrotoxicosis symptoms, or in case of the reappearance of cardiac

rhythm disorders. Corticoids are indicated especially for type II amiodarone-associated thyrotoxicosis, since they reduce inflammation.<sup>2</sup>

No strictly standardised medical treatment has been proposed in the literature. Various treatment strategies are suggested according to the type of thyrotoxicosis.<sup>8</sup> Carbimazole and potassium perchlorate are recommended for the treatment of type I thyrotoxicosis before possible final treatment with radioactive iodine. The corticoids are more suitable for type II amiodarone-associated thyrotoxicosis.<sup>3</sup>

The use of a combination of these drugs should be discussed on a case by case basis.

Indications for the therapeutic administration of radioactive iodine are poorly documented. We consider this treatment to be unsuitable for amiodarone-associated thyrotoxicosis, since in our experience antithyroid treatment is either effective or a failure, in which case thyroidectomy is indicated. In fact, it is harmful to wait for the effects of radioactive iodine to become evident, as this takes even longer than usual since the thyroid is already saturated with iodine. We believe such treatment represents a false promise, which, in our 10th patient's case, delayed the decision to perform a thyroidectomy and thus only worsened the situation. Despite barely elevated free T4 levels and the discontinuation of amiodarone for six months, patient 10 progressed to multiple organ failure. This was probably due to an 18 mm toxic extirpative nodule, which appeared after the diagnosis of amiodarone-associated thyrotoxicosis leading to hyperthyroidism.

However, drug tapering in cases of thyrotoxicosis requires six to eight weeks, and the effects of amiodarone persist for up to eight to nine months after discontinuation because of its long half-life.<sup>9–11</sup> In addition, the discontinuation of amiodarone can be associated with a paradoxical worsening of thyrotoxicosis. In certain patients, treatment with amiodarone cannot be discontinued because of the severity of their cardiac rhythm disorder, especially in the case of complex ventricular arrhythmias. In other patients, the clinical situation is more serious and it is impossible to wait for the period required for effective antithyroid treatment; thus, total or subtotal thyroidectomy is proposed.

This method allows a quick recovery from thyrotoxicosis, enabling the reintroduction of amiodarone once thyroidectomy has been performed. Paradoxically, this life-saving surgery, performed on patients with thyrotoxicosis and underlying cardiopathy, often has a low specific morbidity and mortality rate.

Approximately 100 cases (including our series) have been published worldwide since 1985.<sup>12,13</sup> Of these 100 cases, only three deaths have occurred (in the Mayo Clinic series).<sup>14</sup> One of these deaths was the result of a cerebrovascular accident secondary to a carotid thromboendarterectomy performed at the same time as the thyroidectomy due to the presence of an associated asymptomatic carotid stenosis. The

second case concerned a patient on dialysis with a left ventricular ejection fraction that had decreased to 15 per cent. The last case concerned a 54-year-old man with major heart failure (with a left ventricular ejection fraction of 10 per cent) who was awaiting a heart transplant. These data represent a global mortality rate of 2 per cent. In Gough's series of 14 patients, four were awaiting a heart transplant.<sup>15</sup> The spectacular improvement resulting from thyroidectomy enabled the removal of half these patients (two cases) from the heart transplant list.

Post-operative follow up was simple in most reported cases.<sup>16–18</sup> Complications such as recurrent laryngeal nerve paralysis and transitory hypocalcaemia are no more frequent than following surgery performed in a euthyroid state. Of the approximately 100 reported cases, no secondary surgery was reported for suffocating haematoma, although emergency surgery was sometimes performed under anti-vitamin K cover (as in our patient 11).

Anaesthetic considerations in the management of patients with a fragile haemodynamic status must be taken into account.<sup>18</sup> These include meticulous pre-operative assessment together with minimalisation of amenable anaesthetic risks.<sup>19</sup> Once the cardiologist and the endocrinologist agree on the surgical indication, they must communicate with the anaesthetist. Surgery should not be delayed based on the hypothesis that the patient is in a hyperthyroid state and that an extension of the duration of pre-operative medical preparation will automatically optimise the patient's condition. In fact, it is because of the patient's delicate status that the intervention should be urgent, and may be life-saving. In some cases, any delay would only serve to aggravate the patient's condition: we note that our 10th patient went from poorly tolerated cardiomyopathy to multiple organ failure (renal, hepatic and cardiac) within 72 hours.

- **Pre-operative medical treatment is needed to limit the surgical complications of thyroidectomy for amiodarone-associated thyrotoxicosis**
- **Worsening haemodynamic status should not delay such surgery**

No specific anaesthetic protocol has proven to be superior for this type of high-risk surgery.<sup>20</sup> Familiarisation with special features is essential for the management of an amiodarone-associated thyrotoxic patient. The potential risk of severe bradycardia and sinus arrest (resulting from the interaction between beta blockers and amiodarone) must be taken into account.<sup>17</sup> The peri-operative use of a fast-acting beta blocker such as esmolol is recommended for episodes of tachycardia.<sup>15</sup> Finally, as a result of the pharmacodynamic modifications caused by

thyrotoxicosis, propofol doses must be increased to obtain effective anaesthetic concentrations.<sup>9</sup>

As far as thyroidectomy is concerned, the distinction between type I and type II amiodarone-associated thyrotoxicosis makes no difference for the surgeon. There are no distinguishing features, unless the procedure is performed in extreme emergency (as in our cases 10 and 11). For some authors, the procedure may even be described as technically simple, because of low vascularisation.<sup>17</sup>

The indications for thyroidectomy in case of amiodarone-associated thyrotoxicosis are as follows: (1) when the cardiologists consider amiodarone to be essential despite thyrotoxicosis; (2) type I or mixed amiodarone-associated thyrotoxicosis, since the thyroid disorder may be similar to Grave's disease and therefore may maintain the thyrotoxicosis to which amiodarone contributes; (3) patients awaiting heart transplant; and (4) failure of antithyroid treatment.

The current difficulty lies in defining the criteria of medical treatment failure in a standardised manner, in order to avoid emergency thyroidectomy. In order to understand these factors, a prospective, controlled study is needed.

## Conclusion

Amiodarone can lead to thyrotoxicosis. Antithyroid medical treatment may be effective in controlling the situation. However, sudden aggravations may occur, and amiodarone discontinuation may not be possible; alternatively, the thyrotoxicosis may become increasingly severe. Treatment with radioactive iodine is contraindicated, since its effective onset is delayed. Thus, thyroidectomy must be considered. In the case of multi-disciplinary management, it is often the cardiologists, in agreement with the endocrinologists, who make the surgical decision. Pre-operative medical treatment remains mandatory in order to limit peri- and post-operative complications. In some cases with acute, severe cardiac deterioration during medical preparation, our findings suggest that surgery should not be delayed, as it is the cornerstone of treatment and can be life-saving.

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