Clinical Thyroidology / Original Paper

European Thyroid Journal

Eur Thyroid J 2017;6:108–112
DOI: 10.1159/000453578

Received: August 15, 2016
Accepted: November 11, 2016
Published online: February 18, 2017

# Successful Pretreatment Using Plasma Exchange before Thyroidectomy in a Patient with Amiodarone-Induced Thyrotoxicosis

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**What Is Known about This Topic?**

- Thyroidectomy is a valid alternative for patients with severe amiodarone-induced thyrotoxicosis, or refractoriness or contraindications to medical therapy. Restoring a euthyroid state prior to thyroidectomy is recommended to reduce the potential perioperative risks.

**What Does This Case Report Add?**

- Therapeutic plasma exchange rapidly reduces circulating thyroid hormone levels, improving a patient's symptoms (in this case suggestive of ischemic heart disease) and plausibly decreasing the perioperative risks associated with thyroidectomy in a thyrotoxic state.

**Keywords**
Amiodarone · Thyrotoxicosis · Plasma exchange · Thyroidectomy

**Abstract**

***Introduction:*** Amiodarone, used for the management of tachyarrhythmias, is associated with both hypothyroidism and thyrotoxicosis. Total thyroidectomy is an effective procedure for promptly reducing circulating thyroid hormone levels. It has been proposed in patients who have severe amiodarone-induced thyrotoxicosis (AIT) or are refractory to medical therapy, or when such therapy is contraindicated. Therapeutic plasma exchange (TPE) may be considered as a pretreatment for restoring a euthyroid state preoperatively, thereby reducing a patient's symptoms and the potential perioperative risk associated with thyrotoxicosis. ***Case Report:*** We describe the case of a 62-year-old man with type 2 AIT who presented with severe unremitting thyrotoxicosis after 8 weeks of medical therapy with glucocorticosteroids, thiamazole, and potassium perchlorate. Given the severity of his presentation, a total thyroidectomy was indicated. TPE was performed preoperatively and was successful in rapidly restoring euthyroidism. This dramatically improved the patient's symptoms which had been suggestive of ischemic heart disease. Subsequently, the patient underwent total

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thyroidectomy under general anesthesia without any major complications. ***Conclusion:*** TPE is successful in rapidly restoring a clinical and biochemical euthyroid state, and may be used to decrease the perioperative risks associated with thyroidectomy in patients with life-threatening thyrotoxicosis or in cases refractory to medical treatment.



## Introduction

Amiodarone is an iodine-rich drug, used in the treatment of various tachyarrhythmias. A well-known side effect is thyroid dysfunction. Overt thyroid dysfunction, either thyrotoxicosis or hypothyroidism, occurs in 14–18% of patients [1, 2]. The incidence of amiodarone-induced thyrotoxicosis (AIT) is up to 12% in areas that are iodine-deficient versus 2% in areas that have sufficient iodine [2]. The mechanism is either due to an iodine excess in preexisting abnormal thyroid glands (type 1) or destructive thyroiditis (type 2) [1–3]. The onset is usually sudden and explosive and may occur early during the first weeks of amiodarone treatment, after several years of therapy or even several months after withdrawal of the drug. This is due to tissue storage of the drug and its metabolites, along with its long half-life [1, 2]. Diagnosis is based on suppressed serum thyroid stimulating hormone (TSH), elevated free thyroxine (fT4), and elevated free triiodothyronine (fT3) levels, in particular, with or without symptoms of hyperthyroidism. A further distinction between the 2 types is made based on the presence of thyroid antibodies, thyroid ultrasonography and color-flow Doppler sonography [1–3]. It is advised to conduct thyroid function control tests before administering amiodarone, 1 and 3 months after the initiation of therapy, and every 3–6 months thereafter [2, 4]. Medical treatment consists of thionamide plus potassium perchlorate (type 1) or glucocorticosteroids (type 2) [1–3]. Worldwide, multiple treatment algorithms have been proposed [2]. Combination therapy with glucocorticoids and thionamide, with or without potassium perchlorate, seems to be an attractive option in mixed or indefinite cases because the difficulty of distinguishing between the 2 types is clearly underscored [5]. Whether or not amiodarone can be safely continued is another area of debate. Definitive surgical management may be required in patients with severe thyrotoxicosis or are refractory to medical treatment, or if medical therapy is contraindicated [1–3]. However, concerns remain about the perioperative morbidity and mortality in thyrotoxic patients with preexisting cardiac disease, as the manipulation of the thyroid gland during surgery can induce a life-threatening thyroid storm. Restoring a euthyroid state prior to thyroidectomy is therefore recommended [4, 6].

## Case Report

We describe the case of a 62-year-old man who presented to his general practitioner with progressive dyspnea, palpitations, and exercise-induced angina for the previous 3 months with associated fatigue, weakness, myalgia, tremor, heat intolerance, excessive sweating, and a weight loss of 15 kg despite a normal appetite. His medical history included atrial fibrillation, diffuse coronary atheromatosis without significant stenosis, and grade 1–2/4 aortic insufficiency with mild diastolic dysfunction. For the last 2 years, sinus rhythm had been maintained with oral amiodarone (200 mg daily). There was no information available about his thyroid function, the presence of thyroid autoantibodies, or thyroid gland morphology before amiodarone had been introduced. He had no personal or familial history of thyroid disease. A routine blood test revealed severe hyperthyroidism with fT4 >40 pmol/L (upper limit of laboratory test; normal values 12.5–21.2 pmol/L), fT3 29.6 pmol/L (normal values 3.9–6.6 pmol/L), and serum TSH <0.015 mIU/L (normal values 0.27–4.20 mIU/L). The patient was referred to the endocrinologist who proposed a diagnosis of severe AIT, and promptly initiated treatment with thiamazole (started at 60 mg/day for the first week, then 40 mg/day) plus prednisolone (40 mg/day, tapered to 30 mg/day). In consultation with his cardiologist, amiodarone was discontinued and replaced by the β-blocking agent sotalol (240 mg/day). Thyroid autoantibodies including antithyroglobulin antibody (TgAb), antithyroid peroxidase antibody (TPOAb), and thyroid-stimulating immunoglobulin (TSI) were undetectable. Thyroid ultrasound showed a diffuse, hypoechogenic, heterogeneous gland with a slightly increased volume of 32 mL without nodules. Color-flow Doppler sonography showed an absence of hypervascularity. Potassium perchlorate (500 mg/day) was added after 2 weeks because of a lack of clinical response. Six weeks after the initiation of medical therapy, thiamazole was switched to propylthiouracil (500 mg daily) and prednisolone was again increased to 40 mg/day because of an unfavorable evolution. Eight weeks after the initiation of treatment, he was referred to the Department of Endocrinology in our tertiary referral hospital with worsening of his hyperthyroid symptoms. Despite optimal treatment adherence, the patient presented with a worsening of exercise-induced angina, dyspnea, palpitations, persistent tremor, heat intolerance, excessive sweating, and further weight loss. At physical examination, the patient had facial flushing and excessive transpiration. He was afebrile and was not in respiratory distress. His blood pressure was 165/100 mm Hg and his radial pulse was fast and irregular. The thyroid gland was tender without a markedly increased volume; no nodules were palpable. There were no signs of Graves exophthalmia. Pulmonary auscultation was normal and there was no peripheral edema. Biochemical evaluation showed fT4 >98.7 pmol/L (upper limit of laboratory test; normal values 11.9–21.9 pmol/L), fT3 18.0 pmol/L (normal values 4.0–6.8 pmol/L), and serum TSH <0.015 mIU/L (normal values 0.27–4.20 mIU/L). Electrocardiography confirmed the clinical suspicion of

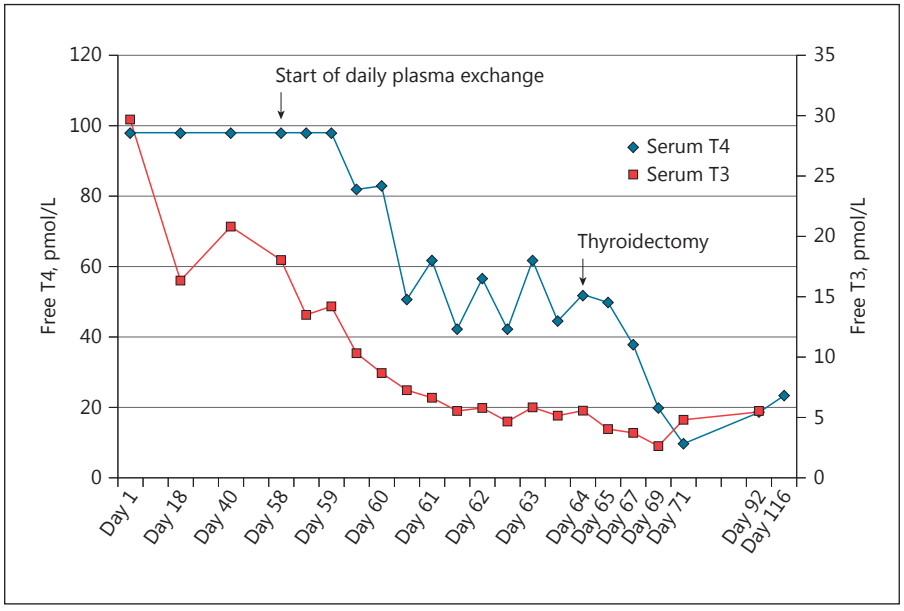


**Fig. 1.** Graphical evolution of thyroid function tests before and during total plasma exchange (TPE) procedures. A total of 6 TPE cycles were required to normalize the free T3 level, after which total thyroidectomy was performed.

recurrent atrial fibrillation with a ventricular response rate of 146 bpm despite high β-blocker dosing. Transthoracic echocardiography showed a preserved left ventricular systolic function. A diagnosis of type 2 AIT was the most plausible, based on the patient's history, the absence of thyroid autoantibodies, and the heterogeneous gland on thyroid ultrasound with the absence of hypervascularity on color-flow Doppler sonography. Thus, additional radioactive iodine-uptake imaging was deemed unnecessary. The patient was considered for definitive surgical management with total thyroidectomy as his clinical symptoms worsened despite 8 weeks of medical therapy. Preoperatively, therapeutic plasma exchange (TPE) was performed with the Spectra OPTIA® apheresis system, to prevent thyroid storm and potential cardiac complications. The Spectra OPTIA device performs a continuous separation through centrifugation and plasma exchange, resulting in high plasma exchange efficiency (80%) [7]. TPE was performed daily and 1–1.5 plasma volumes were exchanged during every procedure. Extracted plasma was replaced with a 5% human albumin solution, except in the last procedure when fresh frozen plasma was used to replenish coagulation factors. Prednisolone was continued at a dose of 40 mg daily. Serum thyroid hormone levels were reduced by approximately 30% after every TPE cycle. The patient mentioned a significant improvement of his symptoms starting from the first 2 cycles. A total of 6 exchanges were performed to normalize his fT3 level. There were no complications related to the plasma exchanges. Thyroid function tests before anesthesia were as follows: fT4 52.1 pmol/L (normal values 12.5–21.2 pmol/L), fT3 5.5 pmol/L (normal values 3.9–6.6 pmol/L), and serum TSH <0.015 mIU/L (normal values 0.27–4.20 mIU/L). A graphical evolution of the thyroid function tests is shown in Figure 1. Total thyroidectomy was performed under general anesthesia with no major intraoperative complications. The dose of prednisolone was gradually tapered over the next weeks and could safely be discontinued. Five days after surgery, the patient was discharged from the hospital in a good general condition. The resected thyroid gland weighed 35.4 g. Histopathological examination demonstrated zones of follicular degeneration, destruction with macrocytic and lymphocytic infiltrates, and some smaller zones of follicular activity (cylindrical epithelium, and colloid and resorption vacuoles). These changes are compatible with type 2 AIT.

## Discussion

We present a case of severe AIT where plasma exchange was successful in rapidly improving the patient's symptoms and reducing circulating thyroid hormone levels. This may have contributed to an event-free thyroidectomy. This report also illustrates the therapeutic dilemma with AIT patients who are considered refractory to conventional medical therapy. The choice of an initial approach combining glucocorticosteroids, thiamazole, and perchlorate is perfectly sound, as mixed or indefinite variants have been reported [1, 2]. Our patient was initially started on a combined regimen due to his severe clinical presentation. Despite 8 weeks of high-dose corticosteroid therapy and good therapy adherence, his symptoms worsened and were suggestive of ischemic heart disease. This prompted us to proceed to total thyroidectomy.

Thyroidectomy has been shown to be effective in the rapid reversal of hyperthyroidism as well as in the improvement of cardiac function in patients with left ventricular dysfunction related to thyrotoxicosis [8, 9]. The procedure is not considered a first-line treatment as concerns exist about surgery-related morbidity and mortality in thyrotoxic patients [8–11]. For instance, in a small

retrospective analysis, patients with severe cardiovascular disease had a higher mortality rate during thyroidectomy for AIT [10]. No perioperative complications were observed, however, in 3 other studies of thyroidectomy in AIT (although in 1 of these, 71% of the patients were prepared for surgery using iopanoic acid) [8, 9, 11]. A recent retrospective analysis of 165 Graves disease patients who were treated with total thyroidectomy did not show a difference in surgery-related morbidity or mortality between the group that reached euthyroidism and the patients who still had hyperthyroidism (42%) preoperatively [12]. Nonetheless, TPE has been proposed as a safe and effective procedure for restoring euthyroidism and preparing patients for thyroidectomy in Graves disease, toxic multinodular goiter, and hyperthyroidism related to iodine excess [13, 14]. Plasma exchange is a procedure where the patient's plasma is extracted and replaced by a colloid replacement solution. During this process, protein-bound substances such as thyroid hormones are removed from the circulation. This induces a shift of intracellular thyroid hormones into the circulation, which are bound onto new binding sites provided by the plasma or albumin replacement solution, thereby effectively decreasing the total thyroid hormone concentrations. In this report, thyroid hormone levels started to decline after the first TPE session, and the fT3 level normalized after a total of 6 cycles. The effect of TPE is only transitory, as illustrated here by the rebound increase of fT3 and fT4 shortly after every plasma exchange cycle (Fig. 1). Plasma exchange should mainly be used in preparation for thyroidectomy because of this transitory effect. It has to be noted that TPE followed by thyroidectomy is only required in a minority of patients, as the large majority of corticosteroid-treated type 2 AIT patients evolve to euthyroidism within the first weeks of medical therapy. This was demonstrated by Bogazzi et al. [15, 17] who observed a mean cure time of 21 and 30 days in 2 different cohorts. Eskes et al. [16] found a similar median time of 4 weeks to normalize the fT4 level. A prolonged treatment time is occasionally needed before euthyroidism is reached. In a prospective study of type 2 AIT patients, a total glucocorticosteroid time of at least 3 months was required in up to 16% of patients before euthyroidism was finally reached [17]. Being able to predict the cure time or probability of response to corticosteroid therapy would allow the early identification of patients in need of more intense treatment. In the model proposed by Bogazzi et al. [17], both baseline serum fT4 >64.5 pmol/L and a normal thyroid volume >12 mL/m$^2$ (normalized for body surface area) were identified as factors greatly increasing the time to reach euthyroidism, and none of the patients with these values achieved euthyroidism within 30 days. Interestingly, these 2 factors were also present in our patient; he had an immeasurably high fT4 level and his normalized thyroid volume was elevated, at 15.9 mL/m$^2$.

Patients with severe thyrotoxicosis and/or underlying cardiac disease should perhaps be more rapidly considered for total thyroidectomy. Whether or not amiodarone is continued, should depend on the prescribed indication. In a retrospective study by Bogazzi et al. [18] on patients with type 2 AIT, the median time to restore euthyroidism was similar, whether or not amiodarone was continued, although a higher rate of recurrent thyrotoxicosis was observed in the patients who did continue amiodarone. In a multicenter study by Eskes et al. [16] on type 2 AIT patients treated with either prednisolone or sodium perchlorate, or both, euthyroidism was reached in all patients despite the continuation of amiodarone, while thyrotoxicosis reoccurred in only 8%.

In conclusion, our case report demonstrates the usefulness of plasma exchange in rapidly restoring clinical and biochemical euthyroidism. The procedure may be used to treat symptoms suggestive of ischemic heart disease related to thyrotoxicosis, and also preoperatively to decrease the potential perioperative risk of thyroid storm. The effectiveness of TPE could prompt a more rapid surgical management in patients with severe thyrotoxicosis or cardiac comorbidity.

## Disclosure Statement

The authors have no potential conflicts of interest to declare.

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