

SHORT REVIEW

Response to adjuvant therapy with potassium perchlorate in amiodarone-induced thyrotoxicosis: observations on three cases

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Received 5 October 2010; accepted 9 December 2010

KEYWORDS

Amiodarone;
Thyroid;
Potassium perchlorate

PALABRAS CLAVE

Amiodarona;
Tiroides;
Perclorato potásico

Abstract

Introduction: Amiodarone-induced thyrotoxicosis (AIT) is a life-threatening, common clinical condition whose clinical signs and response to treatment may vary among patients.

Methods: Three patients treated with amiodarone for atrial fibrillation who developed AIT at least 36 months after starting treatment are reported. Thyrotoxicosis worsened the underlying cardiac conditions and was resistant to treatment with a combination of dexamethasone 8–12 mg/day IV, thioamides 45 mg/day PO, beta blockers, and potassium perchlorate 800–1000 mg/day PO. Two patients achieved sustained euthyroidism after 12 and 32 days of combined treatment, while the third required total thyroidectomy.

Conclusion: A combination of thioamides and potassium perchlorate is an adequate treatment for AIT in patients refractory to thioamides. Use of this combination should be considered for patients with mixed AIT or AIT of unclear etiology.

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A propósito de tres casos. Respuesta a la terapia adyuvante con perclorato potásico en la tirotoxicosis inducida por amiodarona

Resumen

Introducción: La tiroiditis inducida por amiodarona (TIA) es una entidad clínica frecuente, con distintas formas de presentación, respuesta variable al tratamiento, y que puede ser potencialmente fatal.

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Métodos: Se presentan tres pacientes con fibrilación auricular, que desarrollaron una TIA tras al menos 36 meses de exposición al fármaco. El hipertiroidismo asociado no respondió a la terapia farmacológica convencional, conllevando un empeoramiento franco de la cardiopatía de los pacientes, lo que motivó la indicación de tiroidectomía total, previa instauración de una terapia basada en la combinación de dexametasona 8-12 mg/día iv, tionamidas 45 mg/día vo, beta-bloqueantes, junto perclorato potásico 0,8-1 g/día vo. Dos pacientes normalizaron las hormonas tiroideas periféricas tras 12 y 32 días de terapia combinada.

Conclusión: La combinación de tionamidas y perclorato potásico es una alternativa terapéutica eficaz en la TIA tipo I en pacientes refractarios a terapia convencional. Debe valorarse su empleo en pacientes con TIA mixta o etiología no aclarada.

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Amiodarone is an effective antiarrhythmic drug causing thyroid complications in 15% of patients¹. Complications may include hypothyroidism or thyrotoxicosis. There are two types of amiodarone-induced thyroiditis (AIT). Type I AIT consists of an increased synthesis of thyroid hormones, while type II AIT is characterized by inflammation of the thyroid gland with thyroid follicle destruction and the emptying of preformed thyroid hormones into the bloodstream^{2,3}. The differentiation between and management of both conditions is complex. We report three patients with AIT refractory to conventional antithyroid treatment who required adjuvant therapy with potassium perchlorate, with different degrees of clinical response, before definitive treatment with total thyroidectomy.

Table 1 and Figure 1 show the clinical characteristics and type of treatment started, as well as changes in plasma levels of peripheral thyroid hormones in each of the patients.

Case 1

An 84-year-old female patient attended the area hospital for fatigue, dyspnea on minimal effort, palpitations, and insomnia. The patient reported an episode of paroxysmal atrial fibrillation (AF) three years before, which had required electric cardioversion. Treatment was started with amiodarone (200 mg/day) and acenocoumarol. An electrocardiogram (ECG) showed AF with elevated ventricular response (105 bpm). Thyroid function tests showed TSH levels < 0.03 mU/L (normal range, 0.38-4.84) and free T4 (FT4) levels of 4.42 ng/dL (normal range, 0.8-2.0). Prednisone 30 mg/day was started, associated with acenocoumarol, and amiodarone was discontinued. After one month of glucocorticoid treatment with no biochemical response, carbimazole 15 mg/day and propranolol 20 mg/8 h were added. At three months of treatment, the patient showed clear clinical signs of thyrotoxicosis, dyspnea at rest, and a gradual weight loss of 5 kg. In view of the lack of response, our department was consulted, and hospital admission for definitive treatment with total thyroidectomy was decided upon. Physical examination revealed grade 1 goiter with increased consistency and nodular texture, arrhythmic heart rate of 107 bpm (weight 52.8 kg height 1.60 m, body mass index 20.62 kg/m²), jugular vein engorgement, and bilateral ankle and pretibial pitting edema. Thyroid function tests showed a TSH level less than

0.03 mU/L, a FT4 level higher than 7.7 ng/dL, and a FT3 value of 4.6 pg/mL (normal range, 1.8-4.6). A treatment regimen consisting of potassium perchlorate 800 mg/day PO, dexamethasone (DXM) 2 mg/8 IV, carbimazole 45 mg/day, and propranolol 40 mg/day PO was started as a rapid preparation for surgery. The cardiology department started digoxin, and acenocoumarol was continued. At 12 days of treatment with this scheme, patient showed complete normalization of peripheral thyroid hormones, and total thyroidectomy was performed. Patient was diagnosed with type I amiodarone-induced thyroiditis.

Case 2

A 65-year-old male patient was admitted by the cardiology department for angina at rest and sinus tachycardia with long PR for adjustment of treatment. He had a history of type 2 diabetes mellitus, dyslipidemia, arterial hypertension, and mild chronic renal insufficiency. There was also a history of chronic ischemic heart disease with prior revascularization (12 years before) with a dual bypass, and angina at rest for 4 months, which led to placement of 4 stents and stem cell implantation and transmyocardial laser revascularization. The patient had also been treated with amiodarone for several years for episodes of paroxysmal AF. Amiodarone had been discontinued two months before. Echocardiography showed a dilated left ventricle (LV), markedly depressed systolic function (SF), akinesia of septal and anterior segments, and hypokinesia in all other segments. Thyroid function tests showed TSH < 0.03 mU/L, FT4 > 7.7 ng/dL, and FT3 12.8 ng/dL, and our department was therefore consulted. The patient reported no symptoms of thyrotoxicosis, but had lost 15 kg in the two previous months. Physical examination revealed blood pressure of 120-/80 mmHg and a heart rate of 96 bpm, with no goiter, signs of ophthalmopathy, or distal tremor. Carbimazole 45 mg/day and prednisone 45 mg/day were started. After 7 days of treatment, a FT4 level higher than 7.7 ng/dL and a FT3 level of 10.9 ng/dL were found, together with repeated episodes of acute coronary syndrome. Definitive treatment by total thyroidectomy was indicated. Treatment with carbimazole 45 mg/day and dexamethasone 12 mg/day PO was continued, and potassium perchlorate 1,000 mg/day PO was added. After 32 days with this treatment scheme, plasma FT3 levels normalized, and surgery was successfully performed. Severe amiodarone-induced primary

Table 1 Clinical characteristics of patients

	Case 1	Case 2	Case 3
Age (years)	84	65	49
Sex	Female	Male	Female
Amiodarone indication	Paroxysmal AF	Paroxysmal AF	Persistent AF
Exposure time (months)	36	Not determined	36
Signs of thyrotoxicosis	Yes	No	Yes
ECG	AF with ventricular response at 107 bpm	Sinus rhythm at 110 bpm, axis -30° , PR > 20 sec, and poor R progression	Pacemaker rhythm at 60 bpm
Goiter	Yes	Yes	No
Thyroid autoimmunity	Negative	Negative	Negative
Cervical echo-Doppler	Multinodular goiter, Doppler not available	Pseudonodular thyroid enlargement with decreased parenchymal echogenicity and no signal increase in intrathyroid Doppler	Thyroid of normal size with subcentimetric nodules
Tc ⁹⁹ scan	Low uptake	–	Low uptake
Response to potassium perchlorate	Yes	Yes	No
Response time (days)	12	32	–
Histological study	Slightly enlarged, nodular thyroid with some enlarged follicles, areas of fibrosis, and chronic inflammation	Multinodular hyperplasia	Diffuse thyroid hyperplasia, incidental finding of a papillary microcarcinoma (3 cm)
Final diagnosis	Type I AIT	Mixed AIT	Mixed AIT

AF, atrial fibrillation; AIT, amiodarone-induced thyrotoxicosis; ECG, electrocardiogram.

hyperthyroidism of the mixed type was diagnosed. After 12 months of follow-up, the patient had not experienced any more cardiac symptoms.

Case 3

A 49-year-old female patient attended the cardiology outpatient clinic reporting severe asthenia, anorexia, and dyspnea over the previous two to three weeks. She had a history of idiopathic dilated cardiomyopathy dating back four years (NYHA grade II heart failure [HF]), as well as persistent AF diagnosed three years earlier, which was being treated with acenocoumarol and amiodarone, and an automatic defibrillator and a single chamber pacemaker for polymorphic ventricular tachycardia with cardiac resynchronization due to high-grade atrioventricular block had been implanted. Thyroid function tests showed a TSH level less than 0.03 mU/L and a FT4 level higher than 7.7 ng/dL. Amiodarone was discontinued, treatment was started with a beta-blocker (bisoprolol 2.5 mg/day), and diuretic treatment was intensified. Outpatient assessment by our department was requested at this point. A physical examination revealed a HR of 60 bpm, rhythmic heart auscultation with a panfocal systolic murmur, a thyroid gland of normal size and increased consistency, and no signs of HF. Treatment was started with carbimazole 45 mg/day and prednisone 45 mg/day PO. After 15 days of treatment, thyroid hormone levels remained high, and the patient had obvious signs of decompensated HF, including bilateral ankle

edema. Hospital admission for definitive treatment with total thyroidectomy was therefore decided. An intensive scheme consisting of DXM 8 mg/day IV, methimazole 45 mg/day, and potassium perchlorate 1,000 mg/day PO was started. The patient did not respond to treatment, showing gradually worsening signs of HF and the occurrence of steroid myopathy. Despite the persistence of thyrotoxicosis, the poor clinical course of the patient led to the decision to perform total thyroidectomy at 25 days of admission, with no early perioperative complications. The final diagnosis was severe amiodarone-induced primary hyperthyroidism of the mixed type.

Amiodarone is a highly effective class III antiarrhythmic drug with a high iodine content in its molecule. It is a highly lipophilic compound with a wide distribution volume and a long half-life of more than 40 days⁴. Thyroid dysfunction may occur from the start of treatment to several years later^{1,5}.

The clinical signs of AIT are similar to those of thyrotoxicosis for other reasons. However, the signs may partially be masked by the beta-blocking effect of amiodarone and its inhibition of nuclear T3 receptors^{1,6}. Differentiation between both types of AIT is difficult, and mixed types such as those found in two of the reported cases are recognized⁷. Positive autoantibodies, increased thyroid size, thyroid nodules in an ultrasound examination and, mainly, increased vascularization in thyroid echo-Doppler would suggest type I AIT. Scans usually show low uptake in both types because of iodine saturation of the gland. Only the unusual finding of a high uptake suggests type I AIT. Elevated IL-6 levels are found in type II AIT^{2,8}.

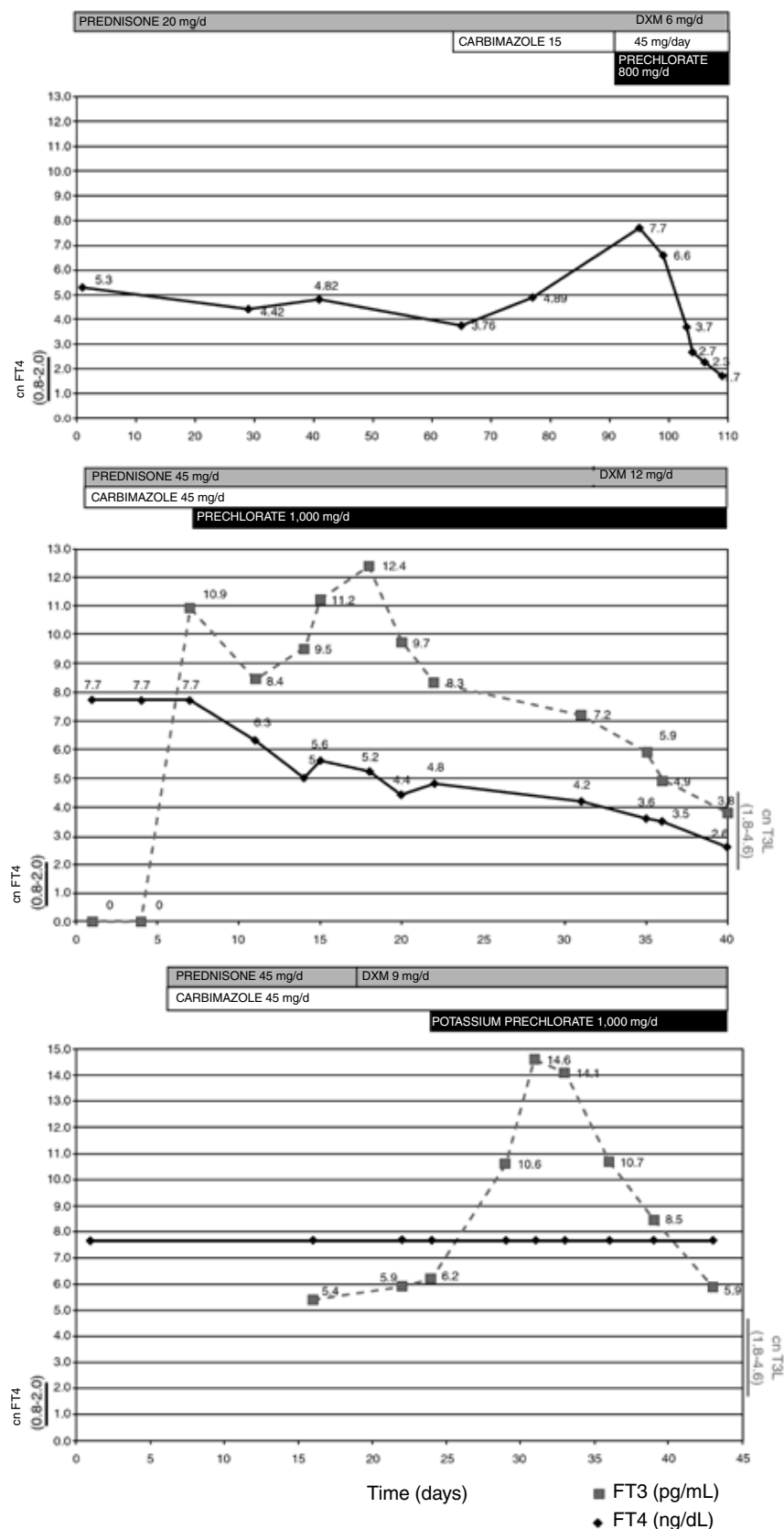


Figure 1 Change over time in peripheral thyroid hormone levels in response to treatment. DXM, dexamethasone; FT3, triiodothyronine; FT4, tetraiodothyronine; NL, normal levels.

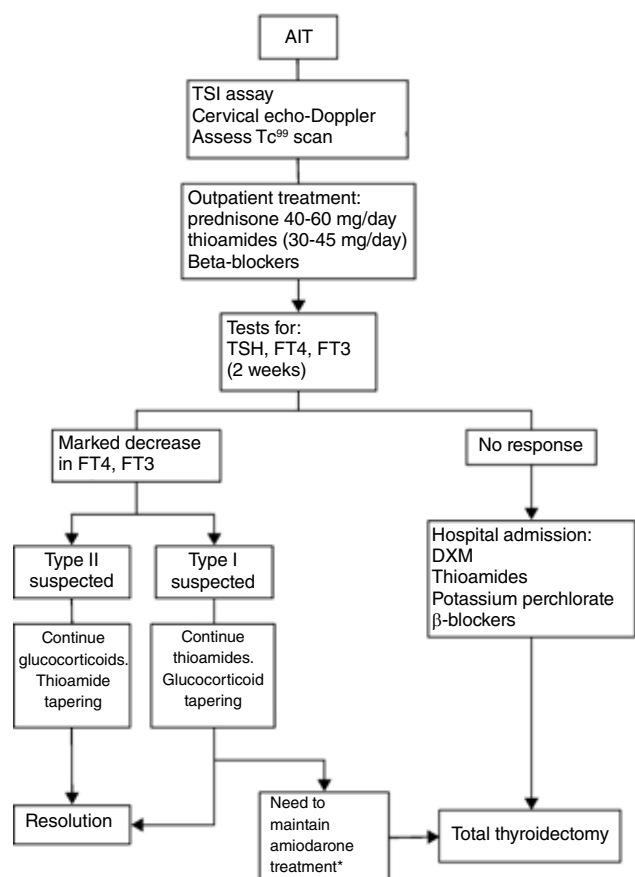


Figure 2 Diagnostic and therapeutic algorithm for amiodarone-induced thyrotoxicosis.

AIT, amiodarone-induced thyrotoxicosis; DXM, dexamethasone; FT3, free triiodothyronine; FT4, free tetraiodothyronine; TSI, TSH receptor antibodies.

*If there is no alternative, effective antiarrhythmic therapy is available.

Type I AIT is treated with thioamides, a drug class that inhibits T4 and T3 synthesis by interfering with the organification of iodine^{1,5,8}. The response is usually slower and occurs at higher doses as compared to other causes of hyperthyroidism with a starting dose of methimazole 30-45 mg/day. The therapeutic approach to type II AIT consists of the administration of glucocorticoids because of their anti-inflammatory and membrane-stabilizing effects. However, in clinical practice it is advisable to start combined therapy with glucocorticoids and thioamides because of the existence of mixed types of hyperthyroidism, the difficulty of initial differentiation of both types, and the need for an aggressive treatment approach leading to rapid normalization of thyroid function in these patients with underlying heart disease (Fig. 2). The addition of potassium perchlorate is recommended in refractory AIT cases².

Potassium perchlorate is a white, colorless, crystalline powder soluble in water which is used together with thioamides for the treatment of iodine-induced thyrotoxicosis. This compound decreases the uptake and concentration of iodine in the thyroid gland through competitive inhibition

of the active transport mechanism ($\text{Na}^+\text{-I}^-$ pump). It also causes a rapid release of iodine accumulated in the thyroid follicles⁹. Potassium perchlorate is indicated for treating type I AIT not responding to thioamides because it increases sensitivity as compared to conventional antithyroid drugs. It may also be helpful in mixed AIT or AIT of unknown etiology. In studies such as the one conducted by Martino et al¹⁰ in AIT patients, only the combination of potassium perchlorate (1 g/day) and thioamides (methimazole 40 mg/dL) was able to control thyrotoxicosis in all treated patients, and euthyroidism was also achieved in a shorter time. These results were confirmed by other studies where euthyroidism was achieved in 2-5 weeks with combined treatment^{11,12}. The main disadvantage of this treatment is its toxicity. Its side effects include nausea and vomiting in some patients, and fever and skin rash have also been reported. Long-term use of potassium perchlorate may cause serious adverse effects (aplastic anemia, agranulocytosis, leukopenia, pancytopenia, and nephrotic syndrome), and frequent hematological monitoring should therefore be performed during treatment. Trotter¹³ compared toxicity of perchlorate and thioamides and found agranulocytosis in 0.3% of 1,200 patients treated with perchlorate and in 0.94% of 1,031 patients treated with thioamides. The adverse event rate with perchlorate was 2%-3%, but increased to 16%-18% with doses higher than 1 g/day¹³. Reports in the literature of 7 cases of aplastic anemia led to decreased use of this compound. However, all of these patients were given doses higher than 1 g/day, and treatment duration before the occurrence of side effects was from 2 to 6 months⁹. These findings have led to a daily oral dose of 600 mg to 1 g in 3 or 4 divided doses being recommended for adults as an initial treatment, followed by maintenance doses ranging from 200 and 500 mg/day in several doses, and for a limited time period^{1,14}. Drug discontinuation is recommended once an euthyroid state is reached, after approximately 6 months of treatment, taking into account that an earlier discontinuation is associated with a high risk of recurrence⁹.

Controversy exists as to whether or not amiodarone treatment should be discontinued, and the potential risks and benefits of discontinuation should be discussed with the cardiologist, as the long half-life of the drug does not result in an immediate benefit and its discontinuation may exacerbate symptoms of thyrotoxicosis because of its beneficial effect by blocking conversion from T4 to T3, β -adrenergic receptors, and T3. There are various studies where drug discontinuation or maintenance did not result in differences in the clinical course of AIT¹⁵. Our experience speaks in favor of amiodarone discontinuation once the initial phase of frank thyrotoxicosis is controlled, provided it is not indispensable for controlling arrhythmia¹.

In patients with thyrotoxicosis due to excess iodine (type I AIT) refractory to conventional therapy, the use of potassium perchlorate combined with thioamides is a safe and effective therapeutic alternative. Patients with mixed forms have variable clinical responses. However, an early start of potassium perchlorate should be considered in patients with associated comorbidities because of the potential morbidity and mortality of AIT in patients with established heart disease.

Conflict of interest

The authors state that they have no conflict of interest.

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