

**Clinical Case Seminar**

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## **A case of amiodarone-induced hypothyroidism in a mild to moderate iodine deficiency area**

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### **Abstract**

Thyroid dysfunction associated to amiodarone treatment depends on iodine intake, as thyrotoxicosis occurs more frequently in iodine deficiency areas, whereas hypothyroidism in iodine sufficient areas. We present here a case of severe overt hypothyroidism induced by prolonged treatment with amiodarone for atrial fibrillation in a man living in a low iodine intake area. The case was managed with levothyroxine (LT4) replacement and amiodarone withdrawal. Euthyroidism was restored after two months, and atrial fibrillation has not relapsed to date.

**KEYWORDS:** amiodarone; hypothyroidism; iodine

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### **Introduction**

Amiodarone is the most used antiarrhythmic drug worldwide [1]. Although considered a class III antiarrhythmic drug capable to block potassium channels, it has also class I, class II and class IV effects, as it blocks sodium channels,  $\beta$ -receptors, and calcium channels, respectively [1]. Amiodarone is a benzofuran compound containing 37% iodine by weight, so that it results in a 20-40 times higher iodine exposure compared to the recommended daily allowance of 150-300  $\mu\text{g}$  [2]. Owing to its benzene ring, amiodarone is highly lipophilic and has a large volume of distribution with delayed onset of action and long half-life (13-142 days) [3,4]. Therefore, it may deposit in different organs such as eyes and lungs [4,5]

In the thyroid, amiodarone acts by different mechanisms, as it inhibits i) T4 to T3 conversion with a decreased clearance of reverse T3, ii) T4 and T3 entry into the cell, iii) and T3 binding to the thyroid hormone receptor type  $\beta 1$  [6]. Amiodarone has also a direct cytotoxic effect on the thyrocyte [7]. Furthermore, high iodine exposure gives rise to either hyperthyroidism or hypothyroidism according to iodine intake. Indeed, in iodine sufficient areas iodine excess results in inhibition of thyroid hormone synthesis and hypothyroidism, whereas in low iodine intake areas it tends to either trigger an underlying Graves' disease (type 1 amiodarone-induced

thyrotoxicosis) or to cause thyrocytes destruction (type 2 amiodarone-induced thyrotoxicosis) [3]. The majority of patients (70%) on amiodarone remain euthyroid, whereas about one third become hypothyroid or hyperthyroid. In contrast with amiodarone-induced hyperthyroidism, which tends to occur in males, amiodarone-induced hypothyroidism occurs more frequently in females (F:M=1.5:1). The major risk factor is Hashimoto's thyroiditis, that is associated to hypothyroidism development *per se*. Females with Hashimoto's thyroiditis are also more likely to develop persistent hypothyroidism when amiodarone is withdrawn [8,9]. In the SAFE-Trial, the rate of subclinical or overt hypothyroidism following amiodarone treatment in an iodine sufficient area was 25.8% or 5.0% [10].

### Case Report

A 73-year old man was referred to our clinic by his sister, a lady with Hashimoto's thyroiditis-associated hypothyroidism, because of weight increase (5 kg), slow speech and fatigue that started about six months before. He lived in Messina, a city of mild-to-moderate iodine deficiency area. Past history taking revealed hypertension treated with ramipril and atenolol and benign prostate hyperplasia, which had been treated with saw palmetto. He also carried a mutation of the coagulation factor VII. Seventeen months before our observation, the man was diagnosed with atrial fibrillation, which had been treated with amiodarone. His thyroid function was checked only 16 months after the beginning of the antiarrhythmic treatment. Indeed, thyroid function test revealed a severe nonautoimmune overt hypothyroidism with extremely high serum TSH (86.9mU/L n.v. 0.25-4.0) and very low FT3 and FT4 levels (1.5 pg/ml n.v. 2-4 and 2.2 pg/ml n.v. 7-19). Antibodies to thyroid (anti-TPO and anti-Tg) were negative. He had never consumed iodized salt at home.

At visit, the patient presented with markedly slurred speech, slow gait, dry skin, puffy face, and delayed patellar tendon reflex. He was slightly overweight (BMI 25.9 kg/m<sup>2</sup>, weight 75 kg). Thyroid ultrasound revealed a normally sized gland (15 ml) with finely inhomogeneous echotexture.

He started LT4 replacement treatment with 25 µg daily dose, which was scaled up to 75 µg/d over 15 days. His cardiologist decided to withdraw amiodarone, while continuing to monitor closely the patient for the risk of relapse of arrhythmia. Two weeks later, TSH dropped to 28.1mU/L, while FT3 and FT4 jumped into the normal range (2.8 pg/ml and 9 pg/ml, respectively). Fatigue was moderate. At visit, his weight was 74 kg and rhythm was sinus. Speech was more fluent. After two months, TSH normalized (2.2mU/L) and fatigue disappeared (**Tab. 1**). To date, atrial fibrillation has not relapsed. We plan to stop LT4 to test whether euthyroidism persists in the absence of LT4 replacement.

**Tab. 1 Summary of thyroid function changes**

Parameter	Normal values	Baseline	15 days on LT4	60 days on LT4
TSH (mU/L)	0.25-4.0	86.9	28.1	2.2
FT3 (pg/ml)	2-4	1.5	2.8	3.0
FT4 (pg/ml)	7-19	2.2	9.0	15.3
LT4 (daily dose, µg)	-	No	25	75

## Discussion.

We have reported a case of amiodarone induced-hypothyroidism in a man living in a mild-to-moderate iodine deficiency area. In low iodine intake areas, where amiodarone gives rise to destructive or autoimmune thyrotoxicosis, hypothyroidism is very uncommon [11]. Unfortunately, we have not assessed urinary iodine concentration, thus limiting any speculation on the degree of iodine deficiency of the patient. Apart from autoimmune hypothyroidism occurring in TPOAb-positive patients, the supposed mechanism whereby amiodarone leads to thyroid hypofunction is the Wolff-Chaikoff effect, namely, high iodine load results in an adaptive blockage of further thyroid iodide uptake and thyroid hormone synthesis [12]. Whenever there is no escape from this phenomenon, hypothyroidism ensues [12]. Perchlorate discharge test has been used for long time to demonstrate this persistent block in intrathyroidal iodine organification [13,14]. For instance, in an Italian study [13], all four patients with amiodarone-induced hypothyroidism who were tested were positive at the perchlorate discharge test. Interestingly, the majority of the 28 patients recruited (19) had an underlying thyroid abnormality, and 10 of them were also TPOAb-positive [13].

Amiodarone-induced hypothyroidism may be transient or persistent, the latter generally being associated to an underlying autoimmune thyroid hypofunction [12,15]. In a Romanian study on 63 amiodarone-treated patients, the authors found 15 cases (23.8%) of hypothyroidism. Interestingly, all 15 patients lived in iodine sufficient areas, and almost half of them were TPOAb positive. Furthermore 11/15 patients (73.3%) had subclinical hypothyroidism [11]. This study confirmed that the pattern of thyroid dysfunction varies according to iodine intake.

In the case reported above the patient was male, tested negative for thyroid antibodies, and lived in a mild-to-moderate iodine deficiency area, all these conditions rendering less likely the development of hypothyroidism compared to thyrotoxicosis. Furthermore, thyroid antibodies negativity led us to assume that amiodarone had been the sole cause of hypothyroidism. We can speculate that the Wolff-Chaikoff effect may have been the culprit in leading to hypothyroidism.

Several authors have suggested checking thyroid function in patients on amiodarone at least every 6 months [15,16]. Indeed, the severity of hypothyroidism probably resulted from the delay in thyroid function testing, the first one having occurred only 16 months after the beginning of the therapy. Amiodarone-induced hypothyroidism is managed with either transient or permanent levothyroxine replacement if thyroid failure is overt (TSH >10mU/L and low FT4). Also, amiodarone ingestion can be maintained, as its withdrawal is not necessary to restore euthyroidism [3]. Subclinical hypothyroidism, especially if associated with TPOAb negativity, can be managed only with a watchful wait, checking periodically thyroid function, as certain patients can regain euthyroidism spontaneously [3]. Furthermore, in elderly patients LT4 treatment has to be used with caution because of the cardiovascular risk associated with LT4 overtreatment. In this regard, perchlorates (either given as potassium or sodium perchlorate), which are inhibitors of the Na<sup>+</sup>/I symporter and are ineffective on the thyroglobulin iodination, may be useful in patients with nonautoimmune hypothyroidism [17]. Bogazzi et al have shown that potassium perchlorate alone was effective in restoring euthyroidism in patients with nonautoimmune hypothyroidism despite amiodarone continuation [17]. In the case presented here, we elected to treat the patient with only LT4 because of the severe hypothyroidism and the difficulty to obtain perchlorates in the market. Also, the severity of hypothyroidism prompted the cardiologist to withdraw amiodarone, while continuing to monitor the patient closely for the risk of relapse of arrhythmia. Nevertheless, as nonautoimmune hypothyroidism induced by amiodarone can be transient, upon euthyroidism has been restored, stopping LT4 should be taken into consideration.

In conclusion, this case demonstrates that although infrequently, amiodarone-induced thyroid dysfunction is hypothyroidism instead of the much more frequent hyperthyroidism. Therefore, regular thyroid function testing of patients on amiodarone is essential to promptly detect any kind of thyroid dysfunction.

**Conflicts of Interest:** There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

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