CASE REPORT

Amiodarone Induced Thyrotoxicosis in the Context of Severe Coronary Heart Disease: A Case Report

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ABSTRACT

Amiodarone is a widely used antiarrhythmic agent, which yields large amounts of Iodine in the organism via its metabolism and has a high elimination half-life. One of the most severe side effects is thyroiditis which can present either as hypothyroidism or as hyperthyroidism. Hyperthyroidism can be further divided into Type 1, for which we use thionamides and Type 2, for which we use glucocorticoids. Interestingly, there are some cases that present as mixed Type 1/Type 2 that need combined treatment. We present here a patient who was on amiodarone and developed mixed type Amiodarone Induced Thyrotoxicosis (AIT) in the context of severe coronary heart disease. Combined treatment should be the initial choice in patients with severe cardiovascular disease.

Key words: Amiodarone; thyrotoxicosis; hypothyroidism; hyperthyroidism

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INTRODUCTION

Pharmacodynamics and pharmacokinetics

Amiodarone is a category-III antiarrhythmic agent (blocks K^+ channels), comprised by 37.5% of Iodine, structurally similar to T3 and T4,[1] yielding 3 mg I_2/100 mg amiodarone when metabolized in the liver.[2] If the daily dose is about 200 mg, it yields 75 mg of organic I_2 in the organism.[1] As a result, 6 mg of free I_2 are being released in the circulation daily, through its metabolism, while the daily needs are about 0.15-0.30 mg I_2.[3] Amiodarone's metabolite, desethylamiodarone, is also active.[1] Amiodarone is highly deposited to the tissues, and has a half-life time ($t_{1/2}$)=10-100 days,[1] mainly due to its storage to the adipose tissue.[3]

Side effects

Amiodarone's most severe side effects include thyroiditis (either hypothyroidism or hyperthyroidism), pulmonary fibrosis and hepatitis. Amiodarone can also cause QT interval prolongation, which can potentially result in torsades de pointes, phlebitis, photosensitizing rash, gray discoloration of the skin (Blue-Man Syndrome) and corneal deposits. 89% of individuals, who started amiodarone, still remained euthyroid after six months of the initiation of therapy, in a retrospective study of 76 individuals.[4] The thyroid effects can be divided into intrinsic drug effects and Iodine-induced effects.[1] The former arise from the inherent properties of amiodarone and include 5'-deiodinase inhibition (thus, total and free T4 and rT3 will increase, while T3 will decrease), inhibition of the entry of thyroid hormones in the peripheral tissues, TSH levels elevation, competitive binding to the T3 receptors and direct damage to the follicular cells.[1] TSH increases about 20-50% acutely, but remains normal chronically.[1] The latter can be attributed to the large I_2 load. These include hypothyroidism, in individuals with pre-existing Hashimoto's disease or by accelerating the course of a pre-existing disease, as well as hyperthyroidism, in individuals with pre-existing autonomous nodules or latent Grave's disease, resulting in uncontrolled hormone synthesis.[1]

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A 49 year old male had suffered an acute myocardial infarction on 01/09/2015. A pacemaker with an automatic defibrillator was placed and amiodarone therapy was initiated. Two months later he was diagnosed with hyperthyroidism. Initially considered to be Amiodarone Induced Thyrotoxicosis (AIT), he was prescribed with prednisolone. Due to poor response, prednisolone was stopped and carbimazole was initiated (40 mg/day divided in 2 doses). The response to carbimazole was also poor and the patient's hyperthyroidism aggravated resulting in nausea, vomiting, jaundice and loss of taste.

The patient was admitted in the cardiology department in February 2016 (due to supraventricular tachycardia and inappropriate defibrillator discharges) in order to properly set the defibrillator. Amiodarone was stopped at that time. The patient was transferred to the Endocrine department. Laboratory values on admission are listed in Table 1. Ultrasonography revealed a diffusely increased in size, highly heterogeneous and strongly micronodular and vascularized thyroid.

TREATMENT

Combination therapy with propylthiouracil (PTU) (600 mg/day, in three doses) and hydrocortisone (100 mg, b.i.d) was initiated. His clinical status improved and hydrocortisone was stopped after 30 days of treatment. Two months later, euthyroidism was reinstituted and thyroidectomy was avoided. PTU therapy was continued for 18 months and resulted in complete remission of hyperthyroidism.

DISCUSSION

Amiodarone Induced Thyrotoxicosis (AIT) can be divided into type 1 and type 2. The main differences between them are shown in Table 2.

Thionamides (carbimazole, methimazole, propylthiouracil) are considered as the drug of choice for AIT1 that usually presents in individuals with pre-existing autonomous nodules or latent Grave's disease. They inhibit Thyroid Peroxidase, thus decreasing the tyrosine iodination. Propylthiouracil also blocks 5'-deiodinase, thus decreasing

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Table 1: Lab Values on admission

FT3	18.1
FT4	100
FT3/FT4	5.4/100
TSH	0.005
Uric Acid	13.9
SGOT	66
SGPT	82
Phosphate	7.5

Table 2: Type 1 AIT vs Type 2 AIT[1-3,21]

	Type 1 AIT	**Type 2 AIT**
Pathophysiology	Big amount of I_2 → elevated production of T3 and T4 (Jod Basedow effect)	Thyroid follicles' Destruction → release of the preexisting T3 and T4
Preexisting Pathology	Yes (nontoxic multinodular goiter or latent Graves' disease)	No
TPO-Ab (Thyroid Peroxidase Andibodies)	Yes	No
Severity	More Severe	Less Severe
Epidemiology		More frequent in Iodine sufficient areas
Serum IL-6	Normal or low	Elevated (only in Iodine –deficient parts of the world)
Radioiodine Uptake (RAIU)	Low	Very low
ECHO findings	Goiter, Grave's Disease	Heterogeneous gland
^{99m}Tc-sesta MIBI	Diffuse Retention	NO significant uptake
Treatment	Thionamides (mainly)	Corticosteroids
Subsequent Hypothyroidism	No	Yes

peripheral conversion of T4 to T3, resulting in a more prompt clinical effect.

Glucocorticoids (prednisone or hydrocortisone) are considered as the drug of choice for AIT2 that resembles the destructive thyroiditis of iodine induced thyrotoxicosis. Contrary to what was done in our case, discontinuation of amiodarone is not necessary.[5] Glucocorticoid doses should be maintained relatively high over a considerable amount of time (1-2 months) in order to avoid exacerbation of hyperthyroidism.[6]

For cases of mixed AIT, with a poor response to monotherapy, a mixed treatment should be attempted. This can be done either as a "stepwise" therapy, with initiation of the first drug and addition of the second in case of no response,[7] or by initiating both anti-thyroid medication and prednisone simultaneously.[8] In case of a rapid response, an AIT2 is more likely the diagnosis. Otherwise, the administration of both drugs should be continued, until euthyroidism is reached. In case of very persistent AIT that neither monotherapy (anti-thyroid drugs or glucocorticoids) nor combined therapy are effective, lithium,[9] plasmapheresis,[10,11] or ultimately thyroidectomy,[12,13] especially in a life-threatening AIT[14,15] should be performed. In the last case, there is a high risk for thyroid storm and arrhythmias, which can be decreased by using Iopanoic acid prior to surgery (not available in the USA),[16,17] or performing the thyroidectomy under local anesthesia.[18,19] There is a need of preoperative treatment in order to reduce the surgical complications of thyroidectomy in such AIT cases, but the worsening hemodynamic status should not delay the surgical removal.[20]

AIT can develop after amiodarone withdrawal and the major risk factors are

1. Hypothyroidism during amiodarone therapy,

2. Larger cumulative dose of amiodarone and

3. Longer duration of amiodarone administration.

As a result, a 24-month follow up of the thyroid function is recommended.[21,22]

Measurement of serum TSH, free T4 and anti-TPO antibodies, before amiodarone initiation should be considered, especially in high risk patients for thyroid disease.

Finally, contrary to what was done in this case, when AIT develops amiodarone discontinuation is not mandatory (as the drug's $t_{½}$ is too high and as such, hyperthyroidism wouldn't subside) and may even aggravate cardiac manifestations (as amiodarone not only inhibits the I-5 deiodinase, thus inhibiting the T4 to T3 conversion in peripheral tissues, but has also beta-blocking effects).

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