

Case report

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**FROM PREVENTION TO PROVOCATION - ELECTRICAL STORM CAUSED BY AMIODARONE
IN PATIENTS WITH AN IMPLANTABLE CARDIOVERTER DEFIBRILLATOR**

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Patients with heart failure (HF) and reduced left ventricular ejection fraction are at increased risk of life-threatening ventricular arrhythmias (VA) and sudden cardiac death. Implantable cardioverter-defibrillators (ICDs) significantly improve survival in these patients, while antiarrhythmic drugs are used to reduce arrhythmia burden and ICD shocks. We present a 67-year-old patient with dilated cardiomyopathy and an ICD, who developed an electrical storm caused by amiodarone-induced thyrotoxicosis (AIT) and experienced more than 3 appropriate ICD shocks for ventricular fibrillation within 24 hours. Laboratory findings revealed severe hyperthyroidism with suppressed TSH and markedly elevated free thyroxine levels. Amiodarone was discontinued, electrolyte abnormalities corrected, HF therapy optimized, and corticosteroids and antithyroid medication treatment initiated. The patient stabilized without further VA. This case highlighted the importance of regular thyroid function monitoring during amiodarone therapy and careful assessment of indications, particularly in patients with ICDs and HF, and its use only in secondary prevention of VA.

Keywords: amiodarone-induced thyrotoxicosis, electrical storm, implantable cardioverter-defibrillator, ventricular fibrillation, heart failure

**OD PREVENCIJE DO PROVOKACIJE: AMIODARONOM IZAZVANA ELEKTRIČNA OLUJA KOD
PACIJENATA SA IMPLANTABILNIM KARDIOVERTER DEFIBRILATOROM**

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Bolesnici sa srčanom slabošću (SS) i sniženom ejekcionom frakcijom leve komore imaju povećan rizik od životno ugrožavajućih ventrikularnih aritmija (VA) i iznenadne srčane smrti. Implantabilni kardioverter-defibrilator (IKD) značajno poboljšava preživljavanje ovih pacijenata, dok se antiaritmijski lekovi koriste za smanjenje učestalosti aritmija i broja IKD elektrošokova. Prikazujemo vam slučaj 67-godišnjeg pacijenta sa dilatatornom kardiomiopatijom i ugrađenim IKD-om kod koga se razvila električna oluja zbog amiodaronom-indukovane tireotoksikoze (AIT). Pacijent je za 24 časa doživeo više od tri opravdana IKD elektrošoka zbog ventrikularne fibrilacije. Laboratorijske analize su pokazale izraženu hipertireozu sa suprimiranim TSH i značajno povišenim vrednostima slobodnog tiroksina. Primena amiodarona je obustavljena, korigovani elektrolitni poremećaji, optimizirana terapija SS i započeto lečenje kortikosteroidima i tireosupresivnim lekovima. Nakon sprovedene terapije postignuta je stabilizacija bez novih VA. Ovaj slučaj ukazuje na značaj redovnog praćenja funkcije štitne žlezde tokom terapije amiodaronom i njegovu opravdanu primenu samo u sekundarnoj prevenciji VA.

Ključne reči: amiodaronom-indukovana tireotoksikoza, električna oluja, implantabilni kardioverter-defibrilator, ventrikularna fibrilacija, srčana slabost

INTRODUCTION

With the extension of the life expectancy of the population and cardiac patients, due to modern diagnostics and treatment, there has been an increase in the incidence of heart failure (HF). Mortality is still unacceptably high (50% in 5 years) despite advances in diagnosis and therapy. In patients with New York Heart Association (NYHA) functional class IV, the reason for death is resistant HF. In contrast, in patients with NYHA class II and III, the reasons are mainly ventricular heart rhythm disorders (1). In this group of patients, where the left ventricular ejection fraction (EF) is below 35%, the benefit of implantation of implantable cardioverter defibrillators (ICD) compared to antiarrhythmic therapy has been proven (2). Speaking of therapy, beta-blockers are the basis for HF and heart rhythm disorders. Amiodarone, as a powerful antiarrhythmic drug, is used in the secondary prevention and therapy of life-threatening ventricular arrhythmias (VA) in patients with reduced left ventricular function when beta-blockers don't give a satisfactory effect. However, with all its advances, amiodarone also brings numerous side effects, such as damage to the thyroid gland (3).

THE AIM

This article aims to present a case of amiodarone-induced thyrotoxicosis (AIT) and to highlight complications associated with the use of this drug in the primary prevention of heart rhythm disorders in patients with poor left ventricular function and an implanted ICD, as well as the treatment of this life-threatening condition.

CASE PRESENTATION

A 67-year-old male patient was referred from a local healthcare center due to multiple ICD shocks. The interrogation of his ICD revealed more than 3 appropriate shocks for ventricular fibrillation (VF) within 24 hours, meeting the criteria for an electrical storm. The medical history of this patient revealed that back in 2020, he had an implantation of a *Medtronic Revia* ICD as a primary prevention of sudden cardiac death due to dilated cardiomyopathy and left ventricular ejection fraction (LVEF) below 35%. Coronary angiography showed normal epicardial arteries, and until the current event, there had been no ICD activations. Current therapy included administration of the following drugs in the form of tablets: Bisoprolol 2.5mg twice daily, Amiodarone 200mg once

daily, Lasix 40mg two tablets every morning, Spironolactone 25mg twice daily, and Ramipril 1.25mg twice daily.

Findings during admission to the coronary unit: ECG monitoring showed sinus rhythm with the corrected QT (QTc) interval of 430 ms, blood pressure was 105/60 mmHg, and oxygen saturation was 91%. Focused echocardiography demonstrated LVEF of 40%. Auscultation revealed bilateral basal crackles without peripheral swelling. Before laboratory results, initial therapy was given to the patient and included oxygen therapy 4L/min, amp. Bensedin 10mg intramuscular (IM), amp Lasix 20mg/12h intravenous (IV), and amp. Presolol 5mgx3. After this, until stabilization, we applied tablets of 40mg Propranolol four times daily, amp. Amiodaron 200mgx6 IV/24h, and amp. Mg 1mg IV. Laboratory findings have been presented in Table 1.

Table 1. Laboratory findings

Potassium	3.3 mmol/L
Sodium	135 mmol/L
Magnesium	1.5 mmol/L
Urea	9.8 mmol/L
Creatinine	128 mmol/L
Creatinine clearance	68 ml/min.
pH	7.37
Troponin	0.100 ng/L
BNP	3280 pg/ml
TSH	0.001 mIU/L
FT4	74.2 pmol/L
CRP	9.8 mg/L

Amiodarone was discontinued due to thyrotoxicosis, as well as the previous inappropriate decision to use it for primary prevention of VA, particularly since the patient's LVEF had improved compared to the time of ICD implantation. Potassium supplementation was initiated targeting levels ≥ 4.5 mmol/L. Guideline-directed HF therapy was continued, and an SGLT-2 inhibitor was introduced. Treatment for mixed-type amiodarone-thyrotoxicosis was started using IV corticosteroids and oral antithyroid medication. The beta-blocker dose was increased (Bisoprolol 5

mg twice daily) and a new antiarrhythmic agent (Minsetil 200 mg three times daily) was introduced.

At the patient's personal request, he was transferred to his local healthcare institution on his second day in hospital. When he was discharged, there were no VA detected on ICD interrogation.

DISCUSSION

The result of HF may come from diseases affecting the myocardium, pericardium, endocardium, valves, or metabolic disorders involving either the left or right ventricle. Based on the left ventricle EF, HF is classified as HF with reduced EF (HFrEF) ($EF < 40\%$), and HF with preserved EF (HFpEF) ($EF > 50\%$). The most common causes of death in HFrEF patients are progression of heart failure and sudden cardiac death, most often due to ventricular tachycardia (VT) or ventricular fibrillation (VF). Patients with NYHA II/III usually die suddenly, whereas NYHA IV patients predominantly die from progressive heart failure. Modern treatment includes optimal medical therapy together with ICD implantation, because ICDs detect and treat the VA both in primary prevention (patients without previous cardiac arrest) and secondary prevention (patients who survived previous cardiac arrest). Multiple randomized studies have demonstrated superiority of ICD therapy over antiarrhythmic drugs in reducing mortality in this patient population (4). However, ICD implantation does not treat the underlying heart disease but rather prevents sudden cardiac death, and it should be emphasized that ICDs cannot always prevent death, particularly in refractory ventricular arrhythmias (5).

Both appropriate (in VTs or VFs) and inappropriate (in atrial rhythm disorders) ICD shocks may cause myocardial injury leading to microfibrosis and progression of HF (6). In addition, every ICD shock is painful and may negatively affect the patient's psychological status, leading to anxiety or depression. Adequate ICD programming and optimal pharmacological therapy are crucial for reducing ICD shocks. Patients with HF and ICDs receive guideline-directed therapy including beta-blockers, RAAS antagonists, mineralocorticoid receptor antagonists, and SGLT2 inhibitors, all shown to improve survival. After beta-blockers, amiodarone remains a cornerstone in the secondary prevention of sudden cardiac death in ICD patients, and its efficiency has been demonstrated even before the ICD era (7). When combined with beta-blockers, it effectively reduces VA and, consequently, ICD shocks. Amiodarone exerts antiarrhythmic effects from all four Vaughan-Williams classes, but it's associated with numerous adverse effects, especially thyroid

dysfunction due to its direct effect and high iodine content. Therefore, regular monitoring of thyroid function (TSH and FT4) is mandatory before and during the treatment. Patients may develop transient thyroid dysfunction, hypo- or hyperthyroidism. The incidence ranges from 2% to 30%, depending on baseline thyroid status, iodine intake, amiodarone dose, and genetic predisposition (3, 8). These adverse effects are often connected with a high amount of iodine, and the most severe forms are AIT, worsening of existing or emergence of new arrhythmias, worsening of HF, and higher mortality among this group of patients (9).

Excess iodine in the body that occurs during chronic amiodarone therapy is transported to the follicular cells of the thyroid. Normally, when the appropriate intracellular concentration of iodine is reached, further uptake into the cells and the subsequent synthesis of hormones are inhibited until the level of iodine in the follicular cell is normalized (Wolff-Chaikoff mechanism). In patients with already impaired thyroid function, this protective mechanism is lost, so that in those with an existing autoimmune disease (Hashimoto's thyroiditis), there may be a depletion of hormones, an increase in the thyroid gland, and thus hypothyroidism may develop (10). In patients with a nodular enlarged thyroid gland, due to the loss of the protective Wolff-Chaikoff mechanism, there is hyperproduction of thyroid hormones and the appearance of hyperthyroidism (11). In the case of the development of hypothyroidism, the problem is solved by hormone replacement, and such a situation does not require stopping the drug application.

When AIT occurs, the clinical presentation can be masked by the beta-blocking effect of amiodarone, which masks the adrenergic effects caused by the increased presence of thyroid hormones. AIT is more common in women, in regions with less iodine in the diet, or with pre-existing conditions such as goiter or Graves' disease. There are two types of AIT: AIT type 1 – where there is an increased synthesis of thyroid hormones (iodine-induced hypothyroidism), and AIT type 2 – where there is an increased release of T3 and T4 caused by destructive thyroiditis (direct toxic effect of amiodarone on thyroid cells). AIT type 1 is more common in previously diseased thyroid glands (autoimmune disease, nodular goiter), while AIT type 2 usually occurs in previously healthy glands (12). Determining the type of AIT is important for therapy. AIT type 1 is indicated by an earlier onset (after 3 months from the start of amiodarone therapy), the presence of an enlarged thyroid gland, and increased blood flow on color Doppler echo examination of the enlarged thyroid gland. Type 2 is indicated by late onset (more than 30 months after starting amiodarone), the thyroid gland is usually of normal size or slightly enlarged, and the absence of increased blood flow on color Doppler echo examination. A mixed type is also possible, including a

combination of AIT type 1 and AIT type 2 mechanisms of thyroid damage. It is necessary to determine the hormonal status of the thyroid gland before the introduction of amiodarone, after three months from the introduction, and then at intervals of 3 to 6 months (13).

The first treatment dilemma is whether to discontinue amiodarone because of its half-life of more than 3 months, its essential role as an antiarrhythmic, and its beneficial effect in blocking the conversion of T4 to T3 in the periphery. The decision must be individual, with an assessment of the reasons for the introduction of amiodarone. In addition, AIT type 2 responds well to therapy, even with continued treatment with amiodarone (14). In stable patients with type 1, the therapy of choice are thionoamides, while in type 2 the drugs of choice are corticosteroids. In case of a mixed type of damage or an unknown mechanism, both drugs are given in combination. Also, in the case of a very pronounced clinical picture, dual therapy can be started, as well as in patients who do not respond well to monotherapy (8). The initial dose of methimazole is 40 mg in one daily dose until the euthyroid state is reached (3-6 months), the initial dose of the drug PTU is 200-400mg divided into two or three daily doses, the initial dose of corticosteroids is equivalent to 40mg of prednisone once a day for 2-4 weeks, with a gradual reduction in doses over the next 2-3 months. In patients who do not respond to aggressive dual therapy, thyroidectomy is indicated (13). Non-standard therapies include potassium perchlorate and plasmapheresis (15). In patients with heart failure (EF<40%), regardless of the type of damage, thyroidectomy is recommended.

CONCLUSION

Antiarrhythmic therapy in patients with ICDs is essential both for treatment of underlying disease (beta-blockers in HF) and for prevention and reduction of arrhythmias. This reduces the number of ICD therapies (ATP and shocks), thereby preventing myocardial injury, reducing symptoms, and preserving ICD battery life. Beta-blockers are indicated in both primary and secondary prevention of arrhythmias, whereas amiodarone should be reserved exclusively for secondary prevention, with regular monitoring (every 6 months) of potential adverse effects, particularly thyroid hormone levels and TSH. Using the lowest effective dose of amiodarone may also help prevent life-threatening adverse effects associated with this powerful antiarrhythmic drug.

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