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TREATMENT OF AMIODARONE-INDUCED THYROTOXICOSIS RESISTANT TO CONVENTIONAL THERAPY

CASE REPORT

ABSTRACT: Introduction: Amiodarone as an antiarrhythmic medication is necessary in the prevention and treatment of malignant ventricular arrhythmias, however, it can induce thyroid dysfunction. Thyroid dysfunction may be either hypothyroidism or thyrotoxicosis, however, 50% of patients who have used amiodarone are euthyroid.

Case report: A 27-year-old female patient, hospitalized at the Clinic for Endocrinology due to type 2 amiodarone-induced thyrotoxicosis. The patient had previously received amiodarone for two years. At age 25, the patient was diagnosed with dilated cardiomyopathy (EF 25%, EDD/ESD 56-57/47 mm) with mild Ebstein's anomaly, WPW Sy and recorded episodes of nonsustained VT. In order to reduce the risk of sudden death and prevent malignant ventricular arrhythmias, ICD-VR was implanted and amiodarone was prescribed. Treatment with propylthiouracil (PTU) and dexamethasone was initiated after

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thyrotoxicosis was diagnosed. Three weeks after the introduction of PTU, hepatotoxicity was registered, thus the medication was discontinued. Thyrozol, which regulates the hepatotoxicity parameters, was introduced. Sodium perchlorate and glucocorticoid (per os, IV and intrathyroidal) therapy was introduced. The treatment had lasted for fifty days and laboratory signs of thyrotoxicosis were still present, which is why a total of eight plasmapheresis sessions were performed. Each plasmapheresis resulted in a significant decrease in FT4 and a slight decrease in FT3. After seventy two days of treatment, an optimal hormonal status of the thyroid gland was established and total thyroidectomy was performed. Conclusion: Patient was treated for amiodarone-induced thyrotoxicosis (AIT) type 2, which was resistant to conventional therapy for a long period of time. Successful treatment was achieved by applying plasmapheresis although the effect of perchlorate and glucocorticoids application cannot be disregarded.

Key words: amiodarone, thyrotoxicosis, plasmapheresis

DISCUSSION

The term thyrotoxicosis refers to the presence of increased amount of thyroid hormones in the blood (thyroxine and triiodothyronine). The term thyrotoxicosis is often used as a synonym for hyperthyroidism, however, there are subtle differences. Although thyrotoxicosis refers to an increased level of circulating thyroid hormones, it can be induced by drug intake (levothyroxine) or excessive release from thyroid tissue (thyroiditis). Hyperthyroidism refers exclusively to the condition that occurs due to excessive synthesis of thyroid hormones in the thyroid gland.

Numerous drugs can cause the disruption of the thyroid function. The most significant are amiodarone, iodinated contrast agents, lithium, interferon α and interleukin 2.

Amiodarone was first made in 1961 and came into medical use in 1962 for chest pain. However, it was withdrawn from the market in 1967 due to side effects. In 1974, it was found to be useful as a powerful antiarrhythmic and reintroduced to the World Health Organization's list of essential medicines, the most effective and safe medicines needed in the health system.

Amiodarone is a benzofuran derivative containing two atoms of iodine per molecule, which amounts to 37.2% of the molecular weight (75 mg of iodine in a 200 mg tablet). Compared to the daily requirements for iodine of 120-150 mcg, these are significant amounts of iodine that are brought into the body with the medicine. Amiodarone chemically resembles thyroxine, and its binding to the receptors additionally contributes to its pharmacological and toxic effects.

Amiodarone improves the survival of patients with potentially lethal arrhythmias. Namely, amiodarone is the most effective in the prevention and treatment of malignant ventricular arrhythmias in patients with heart failure. In 50% of patients with cardiomyopathy, the cause of mortality is sudden death as a result of ventricular arrhythmias. Prevention of sudden death is one of the most important goals in the treatment of heart failure. The most effective prevention of sudden death due to ventricular arrhythmias in cardiac insufficiency is achieved by using ICD devices. Another measure is the use of antiarrhythmic drugs.

Worldwide, the incidence of amiodarone-induced thyroid problems is estimated at 2% to 24%. More than 50% of patients receiving long-term amiodarone therapy have abnormal thyroid function test results. The effects on the thyroid gland can be in form of amiodarone-induced thyrotoxicosis (AIT) or amiodarone-induced hypothyroidism (AIH). However, most of these patients are euthyroid.

AIT is observed in 10 to 20% of people treated with amiodarone. AIT is more common in areas with sufficient iodine and in women. Two different processes lead to the occurrence of AIT. The first mechanism for the occurrence of AIT is iodine-induced hyperthyroidism (AIT type 1), while the other is destructive thyroiditis (AIT type 2). AIT type 1 occurs primarily in people who already have a thyroid disorder (Grave's disease or multinodular goiter), while type 2 occurs also in the previously healthy gland.

However, both mechanisms may be present at the same time and in the same patient. AIT type 2 is now more common. Small-sized, moderately painful goiter can also be found in AIT type 2. Due to high incidence of AIT it is necessary to regularly monitor the thyroid function in patients treated with amiodarone.

According to the recommendations of the "National Guidelines for Good Clinical Practice for the Diagnosis and Treatment of Thyroid Dysfunction", for the purpose of adequate treatment, it is necessary to determine the type of AIT, and diagnostic procedures provide help with this task. Thyroid ultrasound may show

the presence of goiter, while Color Doppler ultrasound is very important for the differential diagnosis of AIT subtypes. In AIT type 1, vascularity of the thyroid gland is increased, while in type 2 it is decreased or absent. A radioactive iodine fixation test can also provide help in differential diagnosis. In AIT type 2 fixation is low (less than 3%), while in type 1 it is low-normal, normal or increased despite a high iodine content in amiodarone.

In case of AIT type 1, the therapy consists in the use of thyroid suppressants. However, in patients with excess iodine, resistance to thioamides occurs, therefore it is necessary to increase the drug dosage. It is also possible to use low doses of potassium perchlorate in a period of 2-6 weeks.

AIT type 2 is to be treated with glucocorticoids in a dosage of 0.5-0.7 mg/kg of prednisone for a period of two to four months.

In patients in whom amiodarone is absolutely indicated and who do not respond to medication therapy, thyroidectomy is indicated when the euthyroid status is achieved.

In the treatment of hyperthyroidism, standard forms of treatment are used, radioactive I-131, thyroid suppressants (propylthiouracil, PTU, and methimazole, MMI), iodine – iodide, glucocorticoids.

The usual initial dose of MMI is 20 to 40 mg per day, usually in a single daily dose. The initial dose of PTU is 200 to 400 mg divided into two or three daily doses. After normalization of thyroxine, which is usually achieved in 6 to 12 weeks from the initiation of therapy, maintenance doses of MMI are usually 100 mg in a single dose per day or 100 to 150 mg of PTU in two to three doses per day.

Iodine – iodide. Iodine is converted in vivo into iodide, which temporarily inhibits the release of thyroid hormones. When thyrotoxic patients are given a high dose of iodine, the symptoms resolve in 1-2 days. The iodine solution in potassium iodide (Lugol's solution) is administered perorally. If its application is continued, the effects reach the maximum in 10-15 days and then decrease. The main application of the drug is the preparation of hyperthyroid patients for surgical intervention and as part of the treatment of severe thyrotoxic crises.

The use of glucocorticoids is required in thyrotoxicosis induced by the autoimmune process, thyrotoxic crisis, and AIT type 2.

In addition to the above standard procedures, in the case of our patient, we were forced to implement a non-standard therapy in addition to glucocorticoids.

The non-standard treatment that we had implemented consisted in the use of sodium perchlorate and plasmapheresis. Sodium perchlorate, i.e. perchloric acid sodium salt is rarely used in the treatment of hyperthyroidism. In cases of severe idiosyncratic reactions to thioamides, agranulocytosis, hepatitis, if an eumetabolic condition is not achieved and application of therapeutic dose of the radioiodine is not possible. Perchlorate is a means by which normalization of the metabolism can be achieved and the patient can be successfully anesthetized and safely operated on. It is used as a solution, usually 8%; it is better to administer a larger number of doses of smaller amounts of solution in order to achieve an even effect. In severe forms of the disease, when hyperthyroidism is very pronounced, 10 to 15 drops are administered 4 to 6 times per day, and the dose is sometimes reduced to a minimum maintenance dose of 5 or less drops 3 times per day. Plasmapheresis is a therapeutic exchange of plasma and it is a useful treatment for many diseases. Positive effects of this procedure are generally observed within a few days. ASFA (American Society for Apheresis) provides a framework for clinical decisions. Costs of plasmapheresis are quite high, in the United States plasmapheresis costs five to ten thousand dollars per session. Sometimes it is necessary to perform the procedure several times. Due to the price it is rarely applied in the USA, and more often in Europe and especially Japan.

CONCLUSION

A 27-year-old female patient was treated at the Clinic for Endocrinology due to AIT type 2. The AIT type was assessed based on the ultrasound examination of the thyroid gland (CD signal not amplified) and negative markers of the autoimmune process (Anti Tg At 0.9 Anti TPO At 1.6; anti TSH Re At <1). The treatment was initiated with PTU which induced hepatotoxicity, thus requiring the discontinuation of the drug. Treatment was continued with glucocorticoids, and upon approval by the Ethics Committee, also with sodium perchlorate, plasmapheresis was repeated several times. After 72 days of treatment, the optimal level of thyroid hormones was achieved in order to perform the surgery as the permanent solution for thyrotoxicosis. Total thyroidectomy was performed. We have achieved the highest efficiency during treatment by applying plasmapheresis, although the effect of sodium perchlorate and glucocorticoids (which did not achieve suppression of the thyroid hormones level without plasmapheresis) cannot

be disregarded. Larger effect of the applied therapy has been observed with regard to FT4, namely, with each plasmapheresis session, the decrease in FT4 was noticeable (larger than in FT3). After the performed thyroidectomy, amiodarone can again be used as the medication for the prevention of malignant ventricular arrhythmias in our young patient with a high risk of sudden death.

Given the long half-life of amiodarone in the body, it is necessary to monitor the thyroid status of patients who had stopped taking the drug, for at least one year after discontinuation. In every patient who experiences worsening of symptoms or recurrence of arrhythmia that was previously well managed with amiodarone, occurrence of AIT should be considered.

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