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Review

AMIODARONE AND THYROID DYSFUNCTION

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SUMMARY – Thyroid gland has a key role in maintaining the body homeostasis. Thyroxine is the main hormone secreted from the thyroid gland, its effect being predominantly achieved after the intracellular conversion of thyroxine to triiodothyronine, which exhibits a higher affinity for the receptor complex, thus modifying gene expression of the target cells. Amiodarone is one of the most commonly used antiarrhythmics in the treatment of a broad spectrum of arrhythmias, usually tachyarrhythmias. Amiodarone contains a large proportion of iodine, which is, in addition to the intrinsic effect of the medication, the basis of the impact on thyroid function. It is believed that 15%-20% of patients treated with amiodarone develop some form of thyroid dysfunction. Amiodarone may cause amiodarone-induced hypothyroidism (AIH) or amiodarone-induced thyrotoxicosis (AIT). AIT is usually developed in the areas with too low uptake of iodine, while AIH is developed in the areas where there is a sufficient iodine uptake. Type 1 AIT is more common among patients with an underlying thyroid pathology, such as nodular goiter or Graves' (Basedow's) disease, while type 2 mostly develops in a previously healthy thyroid. AIH is more common in patients with previously diagnosed Hashimoto's thyroiditis. Combined types of the diseases have also been described. Patients treated with amiodarone should be monitored regularly, including laboratory testing and clinical examinations, to early detect any deviations in the functioning of the thyroid gland. Supplementary levothyroxine therapy is the basis of AIH treatment. In such cases, amiodarone therapy quite often need not be discontinued. Type 1 AIT is treated with thyrostatic agents, like any other type of thyrotoxicosis. If possible, the underlying amiodarone therapy should be discontinued. In contrast to type 1 AIT, the basic pathophysiological substrate of which is the increased synthesis and release of thyroid hormones, the basis of type 2 AIT is destructive thyroiditis caused by amiodarone, desethylamiodarone as its main metabolite, and an increased iodine uptake. Glucocorticoid therapy is the basis of treatment for this type of disease.

Key words: *Amiodarone; Thyroid dysfunction; Amiodarone-induced hypothyroidism; Amiodarone-induced thyrotoxicosis*

Introduction

Amiodarone was synthesized in 1962, and was originally used as an antianginal agent owing to its vasodilating effect[1]. It began to be used as an antiarthritic agent in the 1970s[2]. Today, it is the most commonly used antiarrhythmic agent in Europe and North America[3,4]. It is used in the treatment and prevention of a wide range of supraventricular and ventricular tachyarrhythmias[3,5,6], especially atrial fibrillation (AF)[7,8], ventricular tachycardia (VT) with and without pulse, and ventricular fibrillation (VF)[1,9]. It has been proven as a powerful agent for sinus rhythm maintenance[10], in the prevention of sudden cardiac death, and

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as an adjuvant therapeutic to implantable cardioverter defibrillator (ICD), it significantly reduces the number of ICD shocks[9]. The positive effect of amiodarone in advanced heart failure has also been demonstrated owing to its minimal negative inotropic and relatively small proarrhythmic effect[10-12], and reduction in mortality after acute myocardial infarction[11,13].

Numerous beneficial effects of amiodarone are accompanied by side effects expressed in various organ systems, often limiting its use[14]. Pulmonary and hepatic toxicity, effects on the heart rhythm, and thyroid dysfunction are especially prominent[1,9]. Endocrine abnormalities range from thyroid function test impairments to clinically evident disease, hypothyroidism or thyrotoxicosis[11,15].

Amiodarone

Pharmacology

Although its pharmacodynamics is complex, amiodarone is classified as a class III antiarrhythmic agent according to Vaughan-Williams[3]. Its action is based on blocking repolarization by inhibiting the rapid external potassium current I_{kr}, which is manifested by prolongation of the QTc interval, and atrial and ventricular refractoriness[5,16]. It also blocks Na^+ channels (effect of class I antiarrhythmic agents), β-adrenoceptors (class II effect), and Ca^{2+} channels (class IV effect)[9,17]. The effect on Na^+ and Ca^{2+} channels depends on frequency, so antiarrhythmic activity is more pronounced in tachycardia than in the physiological frequency spectrum[9]. With chronic use of the drug, these effects are potentiated, which results in slowing down of sinoatrial node frequency and atrioventricular node conduction velocity[9,16]. The drug is a benzofuran derivative[18] and is structurally similar to thyroid hormones[19]. The weight content of iodine in an amiodarone molecule is about 37%[20]. Due to the latter characteristics and similarity to thyroid hormones (Fig. 1), in many tissues, including pituitary gland and liver, it acts analogously or antagonistically[5]. Due to its specific composition, the use of amiodarone in a dose of 200-600 mg/day exceeds the recommended daily amount of iodine (150 μg) by 35-140 times, which in combination with structural features of the drug has a specific effect on thyroid physiology[20].

The most important metabolite of amiodarone is desethylamiodarone (DEA), resulting from dealkylation of amiodarone in the liver predominantly through CYP3A4 (cytochrome P4503A4)[17]. DEA, like amiodarone, has an antiarrhythmic effect[9,20]. Both compounds are lipophilic, and extensively bind to plasma proteins[19].

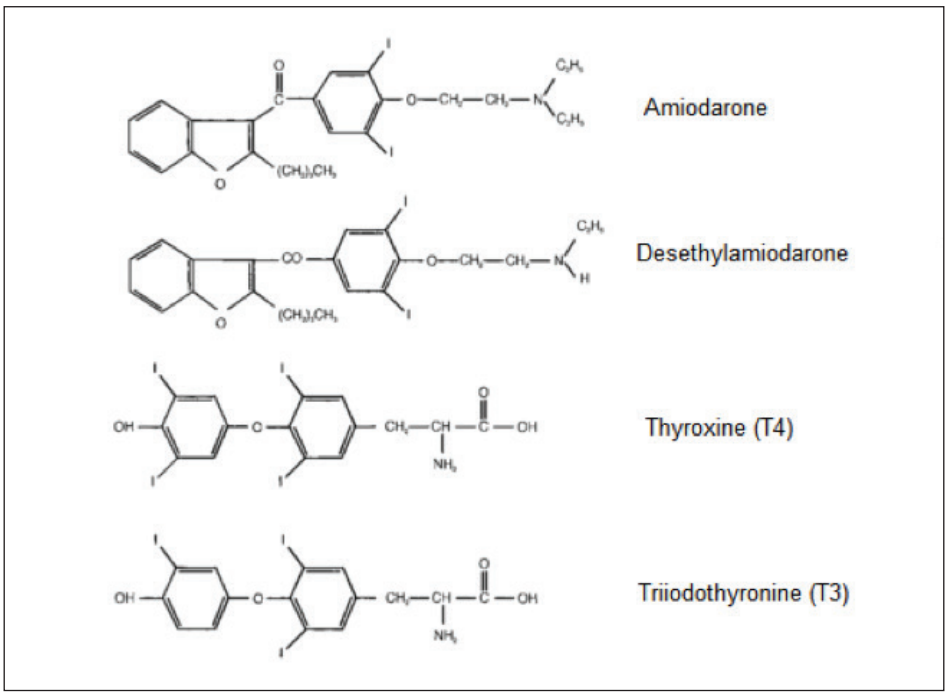

Fig. 1. Chemical formulae of amiodarone, desethylamiodarone, T4 and T3 (adopted from ref. 11).

Drug absorption is poor and variable, while oral bioavailability varies between 22% and 86% (50% on average)[21]. Its large volume of distribution (66 L/kg) contributes to a delayed onset of action (2 days to 3 weeks) and longer elimination half-life[1,21]. The half-life of amiodarone is approximately 40 days, while that of DEA is approximately 57 days, which results in a long-term drug effect after discontinuation of therapy[20].

Both the drug and the active metabolite are distributed in adipose tissue, the liver, lungs, and to a lesser extent in the kidneys, heart, striated muscles, thyroid, and brain[5,20,21]. The vast majority of amiodarone is eliminated by excretion in the bile and stool after metabolism[5,22], with mild renal excretion[9,23].

Untoward adverse effects and toxicity

Amiodarone is considered an antiarrhythmic agent with the most notable side effects[9]. Drug distribution to numerous tissues including adipose tissue, the lungs and liver, long elimination half-life, iodine toxicity, effect on the immune response, and direct cellular toxicity induced by free radicals, and the effects on phospholipids are the causes of potential adverse effects[14,16,24]. Most side effects are reversible through dose reduction or therapy discontinuation[1,7,10]. Side effects manifest in approximately 15% of patients within the first year of treatment and in up to 50% of patients on long-term treatment[10], while therapy is discontinued due to side effects in 13%-18% of patients within the first year of treatment[7,10] and in up to 29% of patients within three years of treatment[14,25].

Cardiovascular side effects are uncommon. The most common one is sinus bradycardia (12.5%), which is expected given the drug mechanisms of action[9]. It mainly occurs in elderly patients, it is dose-dependent, and responds well to dose reduction[7,26]. Although associated with QTc interval prolongation, the frequency of *torsades de pointes* is lower (0.3%) than with other antiarrhythmic agents from class IA and III (0.5-4.7%)[7,9,24,27]. It does not impair the systolic function of the left ventricle[10]. The recommended monitoring of the cardiovascular system includes at least one electrocardiogram (ECG) during the loading dose, especially if an initial disturbance in the conduction system is present. After that, ECG is recommended once yearly[6,7,9].

One of the most severe complications of long-term treatment with amiodarone is pulmonary toxicity[1,7,10,24]. Although it may occur with any dose, the incidence of pulmonary toxicity has been proven to correlate with a cumulative daily dose >400 mg/day[1,14,28] and amounts to <3% of the treated patients[7,10,28]. Other risk factors include male sex, older age (>65 years), duration of treatment >2 years, pre-existing lung disease, and oxygen therapy[9,10,28]. Pulmonary fibrosis is the most severe form of pulmonary toxicity with a mortality of 10%-23%[9]. Treating pulmonary toxicity usually requires discontinuation of amiodarone therapy, supportive treatment, and glucocorticoid therapy[7,28]. Thoracic x-ray and functional lung tests are recommended initially when amiodarone is introduced into therapy, and after that once yearly in asymptomatic individuals. In case of symptom occurrence, it is recommended to repeat testing as needed[1,7,10].

Gastrointestinal side effects most commonly include nausea, anorexia, and constipation. They occur in almost 30% of patients and are most expressed during the loading stage of drug administration, whereas their intensity and frequency decrease during chronic drug use[10].

Increase in liver enzyme levels, i.e., aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (AP), is usually mild, transient and asymptomatic, and is recorded in 80% of the patients treated[9,17,24]. The incidence of more serious side effects such as non-alcoholic steatohepatitis, cholestatic hepatitis and liver cirrhosis is <3%[9,10,24]. It is recommended to perform liver function tests initially, and afterwards monitor transaminase levels every 6 months. Doubling of transaminase levels should be evaluated, and amiodarone discontinued in the absence of other reversible causes[1,10].

Prolonged use of amiodarone can cause blue-brown discoloration of the skin, mainly of the periorbital area and on the face, as well as photosensitivity in up to 75% of patients. These changes occur mainly in the areas not protected from sun exposure, so it is advisable to educate patients on the importance of appropriate sun protection[10,24].

Corneal microdeposits developed in almost all patients who were treated for longer than 6 months. They are mostly asymptomatic, while in a small number of patients haloes appear in the peripheral visual field[11,29]. Optic neuritis is a more severe ocular complication which occurs in <1% of patients. It represents an indication for therapy discontinuation[7,10].

About 30% of patients experience neurological symptoms that include ataxia, tremor, peripheral polyneuropathy, insomnia, and sleep disturbances[7]. They

are generally dose dependent, more common in elderly patients, and in most cases do not require therapy adjustment[7].

The impact of the drug on the thyroid, i.e. on the development of hypothyroidism and thyrotoxicosis, is discussed hereafter.

Effect of Amiodarone on the Thyroid

The effects of amiodarone on the thyroid can be grouped into two major categories, i.e., effects caused by intrinsic drug activity, and effects due to increased iodide release[30].

Effect on thyroid physiology and thyroid hormone status

The majority of initially released hormones are in the form of thyroxine (T4) which acts as a prohormone. Its further conversion into the hormonally active form 3,5,3'triiodothyronine (T3), as well as to other hormonally inactive forms, reverse T3 (rT3) and T2, is catalyzed by a group of selenoproteinases called thyroxine 5'-deiodinases[31,32]. Three isoforms of this enzyme have been described. Type I thyroxine 5'-deiodinase (D1) catalyzes the peripheral activation of T4 into T3, but also deactivation of T4 into rT3[33]. This type of deiodinase is considered to be a secondary source of plasma T3, while its main source is considered to be type II thyroxine 5'-deiodinase (D2)[34]. D2 is also a controller of intracellular T3 concentration[35]. In contrast to type I and type II, the action of type III thyroxine 5'-deiodinase (D3) produces inactive hormonal forms rT3 and T2[36], and is predominantly expressed in the brain, placenta, and fetal tissue[21].

Numerous *in vitro* and *in vivo* studies have established a relation between amiodarone administration and D1 and D2 deiodinase inhibition[32].

By exposing isolated rat hepatocytes to amiodarone, Aanderud *et al.* induced a significant decrease in the conversion of thyroxine (T4) into 3,5,3'-triiodothyronine (T3)[37]. Such a result, as a consequence of inhibition of D1 deiodinase, demonstrated direct dependence on the drug dose administered[37] and is considered to be a consequence of competitive inhibition by amiodarone/DEA[38]. Similar results were obtained by several authors[38,39]. Inhibition of D1 deiodinase can be expected up to several months after discontinuation of amiodarone therapy[21].

Although the effect on hormonal status in amiodarone-treated patients has not been fully clarified and cannot be attributed to a single factor, D2 deiodinase inhibition is now considered to be the dominant mechanism behind these changes[34]. Inhibition of D2 deiodinase in pituitary thyrotropic cells[40], as well as inhibition of the intracellular T3 receptor[41], possibly weakens the effect of the circulating T4 on the inhibition of thyroid-stimulating hormone (TSH) secretion by feedback. This leads to an increase in TSH levels[5,11,21], which is dependent on dose and time, and after prolonged use of the drug returns to normal[5,42].

With increase in the TSH levels, inhibition of deiodinases leads to consequent transient inhibition of conversion of T4 into T3, but also rT3 into T2, which results in an increase in serum T4 and rT3 levels, and a decrease in T3 levels[5]. Therefore, the effects of amiodarone administration may be monitored according to serum rT3 levels[5,43]. Thus, a threefold or fivefold increase in rT3 levels is often associated with a good antiarrhythmic effect, while even higher values are associated with the development of side effects[5,43]. In addition, amiodarone inhibits the entry of thyroid hormones into peripheral tissues[44].

Changes in hormonal status in euthyroid patients treated with amiodarone can be divided into acute, which occur within the first 3 months of drug administration, and chronic, which occur after 3 months of treatment (Table 1)[30]. In a study conducted by Iervasi *et al.*, the dynamics of thyroid hormone and TSH level fluctuation in the initial phase of amiodarone use was assessed. Changes in TSH concentration were evident

Table 1. Effect of amiodarone on thyroid function tests in euthyroid patients (adopted from ref. 30)

Thyroid hormone	Acute effects (<3 months)	Chronic effects (>3 months)
Total T4 and FT4	↑ 50%	↑ 20%-40% above normal value
T3	↓ 15%-20% or lower threshold of normal value	↓ 20% lower than normal value
rT3	↑ >200%	↑ 150%
TSH	↑ 20%-50%, transient increase	Normal

T4 = thyroxine; FT4 = free thyroxine; rT3 = reverse triiodothyronine; TSH = thyroid-stimulating hormone

as early as the first day of monitoring, and by day 10 its level was 2.7 times the baseline value. Levels of total T4 and FT4 had a tendency to rise to a peak value, which was reached on the fifth day of monitoring. In parallel with the increase in TSH levels, an increase in rT3 levels was observed, while T3 levels had a tendency to decrease throughout monitoring, and by day 10 its concentration was approximately 19% of the initial level[30,45].

In the chronic phase, after a 3-month period or longer of drug administration, thyroid hormone levels stabilize, with somewhat altered hormone values relative to the baseline ones. Free T4 (FT4) and rT3 levels remain at the upper threshold of the reference values or elevated, while T3 level remains at the lower threshold of the reference values. It takes up to 12 weeks for TSH levels to return to the reference range[30,46]. Normalization of TSH levels is mediated by multiple mechanisms, whereby an increase in total T4 levels and an escape from the Wolff-Chaikoff effect is thought to play a role, which compensate for the previously developed T3 deficiency and return it to the lower threshold of the normal range[30,47].

The aforementioned changes in thyroid function tests in patients on long-term amiodarone therapy imply standardization of reference values relative to euthyroid individuals who are not on therapy (Table 2)[48].

of rat thyrocytes (FRTL-5), which have iodide accumulation but not organification ability, cytotoxicity has also been demonstrated. These cells demonstrated slightly higher resistance in comparison to the CHO cell line, but in both lines significant lysis began at a concentration of approximately 75 μmol/L. The cells most susceptible to lysis were cultured human thyroid follicles (hTF), which had active iodide accumulation and organification ability. In their case, lysis occurred at a concentration of 37.5 μmol/L. In the latter group, methimazole, a thyroid peroxidase (TPO) inhibitor, statistically significantly reduced cell lysis[11,49]. These results support the fact that amiodarone achieves most of its cytotoxic effect by direct action[49].

The toxicity of DEA is higher than the toxicity of the original drug form, and its concentration in thyrocytes is higher[11,50]. It has also been demonstrated that increased release and accumulation of iodide in thyrocytes induces p53-independent apoptosis, which includes oxidative stress, increased oxygen radical levels, and lipid peroxidation[11,51].

Unlike ultrastructural changes caused by an isolated increase in iodide concentration, amiodarone causes apoptosis, necrosis, inclusion bodies, lipofuscin formation, macrophage accumulation, and endoplasmic reticulum enlargement[52]. Significantly increased expression of endoplasmic reticulum stress markers has also been demonstrated[53]. Moreover, complexes are formed with intralysosomal phospholipids, making them difficult to digest for phospholipases and causing their accumulation. Such a pattern of change, also found in other organs, further suggests the existence of lysosomal storage disease caused by amiodarone[54].

Table 2. Reference values of thyroid hormones and TSH in euthyroid individuals and euthyroid patients on long-term amiodarone therapy (adopted from ref. 48)

Test	Patients not treated with amiodarone	Patients on long-term amiodarone therapy
Free T4 (pmol/L)	11-20	12-24.7
Free T3 (pmol/L)	3-5.6	2.5-5.1
TSH (mU/L)	0.35-4.3	0.35-4.3

T4 = thyroxine; T3 = triiodothyronine; TSH = thyroid-stimulating hormone

Thyroid cytotoxicity

Direct dose-dependent toxicity of amiodarone has been observed in animal and human thyrocyte models[11]. Chiovato *et al.* observed the cytotoxic potential of amiodarone on cells in relation to their iodide accumulation or organification ability[49]. The effect was already observed in the non-thyroid cell line of Chinese hamster ovary (CHO) fibroblast cells, and indicates an intrinsic cytotoxic effect of the drug on cells with proliferative characteristics. In the cell line

Thyroid autoimmunity

The effect of amiodarone on thyroid autoimmunity is debatable. It has been demonstrated on human[11]

and animal models that increased iodine intake can be the cause of autoimmune thyroiditis[55]. Monteira *et al.* conducted a prospective study on 37 patients who had sustained myocardial infarction in the previous 7 to 10 days, and who had not previously suffered from a thyroid disease. Subjects were divided into two groups, one on amiodarone and the other on placebo. In the group of 13 patients treated with amiodarone, 7 (55%) of them developed antithyroid microsomal antibodies *de novo*. None of the patients on placebo developed antibodies. During follow up, 6 months after discontinuation of amiodarone therapy, no previously formed antibodies were found in any of the 7 cases[56].

However, most other studies did not indicate such a direct correlation between amiodarone and the occurrence of thyroid antibodies. Namely, it is believed that amiodarone may accelerate manifestation of a pre-existing autoimmune thyroid disease in susceptible individuals, but without causing the disease *per se*[5,56-59].

Tissue hypothyroidism

Due to inhibition of D1 and D2 deiodinase, amiodarone can cause a condition similar to tissue hypothyroidism. It is believed that this effect is partly mediated by the decrease in the number of catecholamine receptors, but also by a decrease in the effect of T3 on β-adrenergic receptors[11].

Amiodarone and Thyroid Dysfunction

In more than 70% of patients treated with amiodarone, thyroid function is normal, while hormone levels are within the reference values[60]. However, some patients develop thyroid dysfunction, i.e., amiodarone-induced thyrotoxicosis (AIT) or amiodarone-induced hypothyroidism (AIH)[15]. In various studies, the overall incidence of AIT is reported within a wide range of 1%-23%, and of AIH 1%-32%. Thus, the overall incidence of amiodarone-induced thyroid dysfunction is estimated to be 14%-18%[11].

The higher incidence of AIT is specific to iodine-deficient geographic areas[61], whereas AIH occurs more frequently in the areas with sufficient iodine availability[62]. A retrospective study conducted in western Tuscany in Italy (an iodine-deficient region) and Massachusetts in the U.S. (an iodine-sufficient region) found the incidence of AIT to be 9.6% in Italy and 2% in the U.S. Furthermore, the incidence of AIH was 5% in Italy and 22% in the U.S.[63]. Similar results were obtained in a prospective study conducted in The Netherlands, an area with relative iodine deficiency. The incidence of AIT was higher (12.1%) than the incidence of AIH (6.9%)[64].

In Croatia, a retrospective study was conducted at Sestre milosrdnice University Hospital Center on 665 subjects on amiodarone therapy. Among them, 68% of patients were euthyroid. The most common thyroid dysfunction was subclinical hypothyroidism (18%). Of clinically manifest disorders, thyroid dysfunction developed in 14%, AIH in 8%, and AIT in 6% of patients[5].

Other significant risk factors for the development of amiodarone-induced thyroid dysfunction include old age, female sex, complex cyanotic heart failure, Fontan procedure, and daily dose of amiodarone >200 mg[15,65].

Amiodarone-Induced Hypothyroidism (AIH)

Epidemiology and risk factors

Amiodarone-induced hypothyroidism develops in 10%-20% of patients on short-term, and in 5%-10% of patients on longterm (>1 year) amiodarone therapy[20]. Reduction in the prevalence is most likely due to adaptation of the thyroid to the increased iodine uptake[46]. As already stated, it is more common in the areas with sufficient iodine intake, and the ratio of disease-affected women to men is 1.5:1[11,63,64]. Unlike AIT, AIH develops earlier in the course of treatment, and the affected patients are older in comparison to those with AIT[66]. It can develop in a previously healthy or dysfunctional thyroid. With regard to the increase in TSH levels, AIH may be subclinical (TSH 4.5-10 mJ/L), which is a more common form of the disease, and clinical (TSH >10 mU/L)[67].

In a study conducted on 28 patients who developed AIH, it was determined that 19 (68%) of them had a previously known thyroid disease, of which 10 (53%) had positive antithyroid antibodies. Nine out of 28 (32%) patients were previously healthy. This study also demonstrated that the development of long-term hypothyroidism was significantly more common in patients who had previously developed antithyroid antibodies, whereas in previously healthy patients it concerned mostly transient hypothyroidism[62]. In a similar study performed on individuals with positive antithyroid antibodies and ultrasound-confirmed Hashimoto's thyroiditis, during amiodarone therapy lasting for

4 to 9 months, 71% of patients developed clinically manifest hypothyroidism[68].

In view of the aforementioned, the main risk factors for the development of AIH are considered to be female sex and anti-TPO antibodies[68]. According to Trip *et al.*, the relative risk for females is 7.9, and for positive anti-TPO antibodies 7.3. The presence of both major risk factors means a 13.5-fold higher relative risk of developing AIH compared to males without antithyroid antibodies[64].

Pathogenesis

There are multiple theoretical proposals of AIH development. A direct effect of iodine inhibition on the synthetic activity of the thyroid[21,69], the inability to escape the Wolff-Chaikoff effect, or both are plausible[11,21,47]. The Wolff-Chaikoff effect is manifested by a decrease in the synthetic activity of the thyroid, and a reduced release of hormones after an increase in plasma iodide levels[70]. The organification of iodide and thus the synthesis of thyroid hormones is reduced. The effect is manifested after 6-24 hours of iodide level elevation[71]. In a healthy thyroid, it lasts for 3-4 weeks, after which iodide uptake by thyrocytes, as well as iodide inhibition is reduced, which ultimately leads to increased release of thyroid hormones and re-establishment of euthyroidism. This mechanism is called escaping the Wolff-Chaikoff effect[47]. The possibility of escaping the Wolff-Chaikoff effect is not the same in previously euthyroid patients, where this function is mostly preserved, and in patients with underlying Hashimoto's thyroiditis, where it is mostly dysfunctional[30].

A non-specific effect of iodide and amiodarone on thyroid follicles is also possible[72], which is most evident in a thyroid already damaged by Hashimoto's thyroiditis. The latter effect is thought to promote autoimmune inflammation and accelerate the progression of hypothyroidism, which is the natural course of the disease[62].

Clinical presentation

Amiodarone-induced hypothyroidism typically occurs 6-12 months after therapy initiation[69]. Clinical symptoms and signs do not differ from those in hypothyroidism of other etiology[60]. They are not entirely specific and include dry skin, fatigue, weakness, feeling cold, and menorrhagia. Long-term or severe hypothyroidism may also be a cause of ventricular arrhythmia worsening. With lower frequency, AIH may be associated with acute renal failure, which is reversible after levothyroxine treatment and discontinuation of amiodarone[69]. Cases of myxedema coma have also been reported, but such a strong clinical presentation is rare[73].

Diagnostics and treatment

Diagnosis is based on laboratory results and/or presence of AIH symptoms. In subclinical AIH, TSH levels range from 4 to 10 mU/L, FT4 11-19.5 mU/L, while in the clinical form of the disease TSH is >10 mU/L, while FT4 is <11 mU/L[74]. Elevated TSH levels in the first 3 months of amiodarone therapy are not of much benefit as they can also be found in euthyroid patients, whereas a more pronounced elevation (>20 mU/L), despite early results, generally indicates a thyroid disease[30].

Treatment of AIH is based on thyroid hormone replacement with levothyroxine. Discontinuation of amiodarone therapy is often not necessary. The goal of therapy is to keep TSH levels at the upper threshold of the normal reference values[30]. Treatment is started with doses of 25-50 μg of levothyroxine/day, and is gradually adjusted until target TSH values are achieved[20]. A higher dose of levothyroxine is usually required than in the treatment of hypothyroidism of other etiology in order to overcome the inhibition of peripheral conversion of T4 into T3, and the inhibition of type II thyroxine 5'-deiodinase in the pituitary gland[75]. In one study, the mean euthyroidism-maintenance dose in patients with hypothyroidism of other etiology was 136 μg/day, while in patients with AIH it was 256 μg/day[76]. If discontinuation of amiodarone therapy is possible, in patients with a previously healthy thyroid, euthyroidism is achieved within 2-4 months after amiodarone omission, with levothyroxine indication in case of symptomatic hypothyroidism[62]. Due to the possibility of spontaneous remission of hypothyroidism, it is recommended to check the hormonal status in 6-12 months, and reevaluate the need for hormone replacement therapy. Patients with previously positive antithyroid antibodies are more likely to develop long-term hypothyroidism despite discontinuation of therapy[62].

Amiodarone-Induced Thyrotoxicosis (AIT)

Just as it can cause hypothyroidism, amiodarone can also cause thyrotoxicosis. Since patients are primarily cardiac disorder sufferers, any thyroid dysfunc-

tion, especially thyrotoxicosis, can significantly impair previous therapeutic successes and be the cause of underlying heart disease worsening. Depending on the various etiologic, epidemiologic, pathophysiologic and therapeutic specifics, there are two types of AIT, among which a mixed type of disease is also described.

Type 1 develops in persons with a previously known thyroid disease, most commonly latent Graves' (Basedow's) disease or multinodular goiter[30,77,78]. Increased iodine intake is thought to stimulate the synthesis and release of thyroid hormones, and thus lead to a clinically evident hyperthyroidism (Jod-Basedow phenomenon)[48].

Unlike type 1, type 2 develops more often in a previously healthy thyroid[79]. In this type of disease, the pathophysiologic backbone of hyperthyroidism development is destructive thyroiditis[48]. Amiodarone and DEA-mediated tissue damage increases the release of previously synthesized T4 and T3, leading to thyrotoxicosis[48,77,78].

Numerous studies have indicated that there is a significantly increased risk of developing major cardiovascular events in AIT patients in comparison to control groups[80,81]. Elderly patients and those with a reduced left ventricular ejection fraction <45% are particularly at risk[80]. Therefore, achieving euthyroidism is imperative in the treatment of AIT, which opens up a whole range of diagnostic and therapeutic challenges[80].

Epidemiology and risk factors

Amiodarone-induced thyrotoxicosis occurs more frequently in the areas with deficient iodine availability[63]. The incidence ranges between 5% and 10%[69]. Unlike AIH, which is more common in women, AIT occurs predominantly in men with a male to female ratio of 3:1[82]. The occurrence of AIT is less predictable than AIH, and can occur at any time during[64] and 6-9 months after discontinuation of amiodarone therapy. However, it most commonly occurs between 4 months and 3 years of drug use[67]. It occurs earlier in type 1 disease, and later in type 2 disease[83]. If AIT develops after discontinuation of amiodarone therapy, it is more likely to be type 2[83]. In a study conducted in an area with deficient iodine intake, it was found that 38% of patients with AIT previously had multinodular goiter, 29% had nodular goiter, and 33% had a morphologically normal thyroid, which was confirmed by ultrasound[61]. In addition to these features, dilated cardiomyopathy and cardiac sarcoidosis are considered to be risk factors for the development of AIT[84].

Clinical presentation

Amiodarone-induced thyrotoxicosis can present as hyperthyroidism or thyrotoxicosis of other etiology, and there are minor differences in clinical presentation depending on the type of AIT. Weight loss, decreased heat tolerance, fatigue, muscle weakness, somewhat more frequent bowel movements, weight loss, oligomenorrhea, anxiety, depression, and palpitations predominate in clinical presentation[85].

Since this is a disease that predominantly affects elderly population, these symptoms often require additional efforts to be distinguished from those attributed to multiple comorbidities from which patients often suffer[81]. Recurrence of atrial fibrillation or tachycardia and anginal pain in patients treated with amiodarone are often the only signs of the disease onset.

Furthermore, due to the reduced metabolism of warfarin, inhibition of its degrading enzymes by amiodarone and DEA potentiates the anticoagulative effect. Therefore, any need to reduce the dose of warfarin in patients on amiodarone requires re-evaluation of the thyroid[86].

Possible modification in relation to the typical clinical presentation of hyperthyroidism is due to the antagonism of the drug and metabolites to β-adrenergic receptors, inhibition of deiodinases, and blockage of the direct effect of T3 on the heart[87].

Owing to the aforementioned, an asymptomatic course of the disease is possible, which is then detected by regular monitoring of patients. In younger patients, a highly symptomatic form of the disease is also possible, more often in type 2[85]. Orbitopathy is most often not present, while thyroid enlargement can be found in type 1, whereas in type 2 the thyroid is most often of normal size[30].

Diagnostics and differential diagnosis

Diagnosing AIT is more complex than diagnosing AIH. The occurrence of the disease is less predictable, and the clinical presentation is not specific enough, which significantly complicates the approach to a patient with suspected AIT.

In laboratory results, an increase in FT4 levels and a decrease in TSH levels predominate. Given the significance of this result, AIT can be divided into subclinical AIT and clinically evident AIT. In the sub-

clinical form of the disease, TSH levels are within the range of 0.25-0.50 mU/L, while FT4 is within 11.0-19.0 mU/L. In the clinical form of the disease, TSH is <0.25 mU/L, and FT4 is >19.5 mU/L[74]. Increase in the levels of total T4 and FT4 is also possible in euthyroid patients (normal TSH levels) treated with amiodarone. T3 levels may be normal or elevated[30].

These laboratory results are not specific enough to distinguish between different types of AIT, so diagnosis is usually determined by more detailed diagnostics, which is extremely important because of varying therapeutic approaches to different types of the disease[88].

A characteristic of patients with type 1 AIT is that they already have an underlying thyroid disease, most commonly diffuse or nodular goiter, or latent Graves' (Basedow's) disease. Antithyroid antibodies, especially to the TSH receptor, are therefore more common in this type of disease until they are encountered in patients with a previously healthy thyroid. However, since antithyroid antibodies can also be found in 8% of patients with type 2 AIT, they are not considered to be reliable enough for diagnosis and therapeutic approach[89].

The ratio of T4/T3 hormone levels >4 is characteristic of destructive thyroiditis, which corresponds to type 2 AIT. However, the biggest significance of this result is at the population level, whereas it is less so at the individual level due to the already elevated FT4 levels compared to FT3 in amiodarone-treated patients[90].

Results of the 24-hour radioactive iodine uptake (RAIU) test are normal or elevated in type 1 AIT, often >8%[91], which corresponds to the underlying pathophysiological mechanism. This result is significantly lower (<2%) in type 2 AIT[91], where inflammation prevents the physiologic iodide organification. In the areas with sufficient iodine intake, the importance of RAIU is reduced to the extent that lower values are obtained in both types of the disease due to the competition between radioiodine and stable iodine intake[91].

Ultrasound records most often show increased gland volume, hypoechoic tissue structure, and nodular changes in type 1 AIT but normal results in type 2 AIT[85,92]. Since an ultrasound record, despite possible presentation of pathologic changes, does not provide information on functional changes for further orientation, color flow Doppler sonography (CFDS) is used. Today, CFDS is considered to be the gold standard in distinguishing between the two types of the disease, and it is considered that 80% of AIT cases can be interpreted[93]. Detected patterns of increased blood supply to the gland, corresponding to types I, II and III on CFDS, are characteristic of type 1 AIT, whereas type 2 AIT shows reduced blood flow, i.e. pattern 0[94].

In cases that are still doubtful, scintigraphy is recommended with Technetium (^{99m}Tc) sestamibi. Increased accumulation of the radiopharmaceutical is present in type 1 AIT, whereas reduced results are characteristic of type 2 AIT[95]. This method is considered to be suitable for diagnosing even mixed forms of the disease[95]. However, the cost and availability significantly limit the use of this assessment method, which should be reserved for specific cases.

Bartalena *et al.* demonstrated interleukin 6 (IL-6) to be a good indicator of a thyroid destructive process[96]. In type 1, IL-6 levels are normal or slightly increased, whereas in type 2 they are significantly elevated[91].

Finally, from everything that has been presented, it is clear that distinguishing between the two main types and the mixed form of the disease is challenging, even for experienced clinicians. No single result confirms or excludes individual forms of the disease, and the decision on the type of the disease is based on a combination of several diagnostic methods.

Treatment

Treatment of AIT is extremely complex. In therapeutic approach, it is crucial to primarily answer the question of whether amiodarone treatment should be continued in the patient. There is no single answer to this question, and it is necessary to consider the benefit-risk balance in each individual case through an individualized approach. According to the guidelines of the European Thyroid Association from 2018, discontinuation of therapy is not recommended in the treatment of life-threatening arrhythmias or in patients with a poorer prognosis of underlying heart disease, and it is considered that exclusion of amiodarone use in type 2 AIT is more frequent[97]. In addition, the benefit of therapy discontinuation becomes apparent gradually, as both the drug and DEA have a long half-life[98]. Furthermore, due to the blockade of peripheral conversion of T4 into T3, blockade of β-adrenergic receptors, and T3 nuclear receptors, omission of amiodarone from therapy could exacerbate thyrotoxicosis[85]. All patients with AIT, due to increased mortality and morbidity, especially if they are elderly and/or have a reduced left ventricular ejection fraction, are

considered to be potential candidates for urgent treatment of thyrotoxicosis[97].

Treatment of type 1 AIT

Medical therapy

Given the pathophysiologic basis of type 1 AIT, the basic therapeutic principle is to act on the increased synthesis of thyroid hormones. This effect is achieved by thyrostatics[88,97], methimazole/thiamazole and propylthiouracil. High drug doses (40-60 mg of methimazole or equivalent dose of propylthiouracil) and their prolonged use are often required to achieve a satisfactory effect[60]. Due to iodine overload in the thyroid, long half-life of the drug, and the need to establish euthyroidism as early as possible, it is recommended to introduce sodium perchlorate, an inhibitor of thyroid iodide uptake, into therapy[97]. To minimize the side effects of sodium perchlorate, especially on the bone marrow and renal function[11,69,79], the recommended daily dose is limited to maximum 1000 mg[97], with regular blood count monitoring. It is extremely important to educate the patient on the importance of recognizing clinical toxicity of perchlorate in the form of laryngitis, frequent aphthous ulcerations, and fever[77,99]. Furthermore, some authors state that the use of perchlorate is not indicated for more than 4-6 weeks[11,97]. Within this period, iodine overload in the thyroid is expected to decrease, which would increase the efficacy of thyrostatics[77]. If possible, discontinuation of amiodarone therapy is recommended in this type of disease[30,97].

Definitive treatment

After achieving euthyroidism, definitive treatment of thyrotoxicosis should be considered. It is not different from the treatment of thyrotoxicosis of other etiology. Thyroidectomy and radioactive ^{131}I (radioiodine, RAI) are most commonly considered.

The use of radioiodine is possible only after normalization of iodine uptake in thyrocytes, usually 6-12 months after discontinuation of amiodarone therapy[97]. Preliminary evaluation of iodine overload is based on normal results of iodine levels in the urine and accumulation of ^{131}I in the thyroid >10%[20]. This treatment method has demonstrated advantages in the management of patients in whom, due to the initial cardiac pathology, continuation of amiodarone therapy is necessary or should not even be stopped[100].

In patients in whom previous treatment methods have not been successful, total thyroidectomy is recommended[101]. Currently it represents the best option to rapidly establish euthyroidism[102]. This option should be considered especially in patients with reduced left ventricular ejection fraction, as it has been proven that such a diagnosis is associated with increased mortality, while prolonged thyrotoxicosis is associated with accelerated onset of cardiac decompensation[80,97]. Moreover, any deterioration in cardiac function and disease progression are indications for surgical treatment[97].

Treatment of type 2 AIT

The gold standard for treating this form of the disease is the use of prednisone[103]. It achieves its beneficial effect by anti-inflammatory action, membrane stabilization, and inhibition of thyroxine 5'-deiodinase activity[11,21,79]. In some patients with subclinical and milder forms of the disease, spontaneous remissions are possible. It is estimated that 20% of AIT cases, most of which are type 2, resolve spontaneously[20]. With the initial doses of prednisone of 40-60 mg/day, the effects can be observed already during the first week of treatment. However, it is recommended to maintain glucocorticoid therapy for 1-3 months to reduce the likelihood of disease relapse[104]. It is recommended to exclude amiodarone from therapy if possible. In case of emergency, thyroidectomy is indicated as a therapeutic option[97].

Mixed form of disease

The mixed, indefinite form of AIT is not a clinically fully clear entity, and is thought to be the result of combined action of the pathophysiologic substrate of type 1 and type 2 disease[78]. Patients with normal gland morphology, absent enhanced vascularization, and negative anti-TSH antibodies are unlikely to have a mixed form of AIT. Such results point to type 2[97]. However, distinguishing the mixed form of disease from type 1 is more complex, and is based on the exclusion of other differential possibilities.

If diagnosis is still unclear, it is recommended to treat the mixed form of the disease with a combination of prednisone (40 mg/day) and thiamazole/methimazole (40 mg/day). A rapid response to this therapeutic approach suggests type 2 AIT. Methimazole can then be omitted from therapy. In contrast, a poor response to combination therapy suggests type 1 AIT. In this

case, it is recommended to omit glucocorticoid from therapy and to continue treatment as described for type 1 AIT[93].

Monitoring of Thyroid Function in Patients on Amiodarone

Prior to introducing amiodarone therapy, initial assessments should be performed to evaluate thyroid function. These include TSH, FT4 and FT3 levels as needed, anti-TPO and anti-thyroglobulin antibodies, and thyroid ultrasound. Patients with initially elevated TSH levels and/or positive antibodies, as well as ultrasound presentation of Hashimoto's thyroiditis are at an increased risk of developing AIH. Decreased TSH values and ultrasound-confirmed nodular goiter prior to treatment initiation increase the risk of developing type 1 AIT[15].

During amiodarone therapy, it is advisable to monitor thyroid function every 6 months by checking TSH and FT4 levels, and if necessary, by broadened diagnostics[5,11].

Conclusion

The wide range of indications and success of treatment is the reason behind the widespread use of amiodarone as an antiarrhythmic agent. It represents an indispensable drug in the current cardiac approach to the patient. On the other hand, numerous side effects limit its efficacy, while a favorable therapeutic outcome is mostly the result of balancing between the drug multiple beneficial effects and the prevention, early detection, and treatment of its adverse effects. The ungrateful pharmacokinetics of the drug and the marked potential for the development of adverse effects in multiple organ systems are just some of the reasons why increased caution is necessary in the use of amiodarone.

Thyroid dysfunction along with hepatic and pulmonary toxicity occupies a central position among the drug adverse effects. Its high incidence and direct correlation with cardiovascular outcome make it one of the most important entities that is closely associated with long-term amiodarone treatment. Thyroid dysfunction poses a direct threat to preserving cardiac function, especially thyrotoxicosis. If the fact that amiodarone is used to treat various cardiac pathologies is kept in mind, amiodarone-induced thyroid dysfunction may be the onset of *circulus vitiosus*, the prompt treatment of which is of utmost importance to the patient and of extreme complexity to the physician.

In order to promptly detect any abnormalities in thyroid function, regular monitoring of patients is necessary. Any fluctuation in TSH levels or onset of symptoms corresponding to hypothyroidism or thyrotoxicosis requires further diagnostics and timely treatment according to the indication.

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Sažetak

AMIODARON I TIROIDNA DISFUNKCIJA

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Štitna žlijezda zauzima ključno mjesto u održavanju homeostaze cijeloga organizma. Temeljni hormon koji luči je tiroksin, a učinak se dominantno ostvaruje nakon unutarnje konverzije tiroksina u aktivniji oblik, trijodotironin, koji pokazuje veći afinitet za receptorski kompleks te time modificira gensku ekspresiju ciljnih stanica. Amiodaron je jedan od najčešće upotrebljavanih antiaritmika i rabi se u liječenju širokog spektra aritmija, najčešće tahiaritmija. U svom sastavu sadrži velik udio joda, što je, uz intrinzični učinak lijeka, temelj utjecaja na tireoidnu funkciju. Smatra se kako 15%-20% bolesnika liječenih amiodaronom razvija neki oblik tireoidne disfunkcije. Amiodaron može biti uzrokom razvoja amiodaronom izazvane hipotireoze (*amiodarone-induced hypothyroidism*, AIH) ili amiodaronom izazvane tireotoksikoze (*amiodarone-induced thyrotoxicosis*, AIT). AIT se češće razvija u područjima sa smanjenim, dok se AIH razvija u područjima s dovoljnim unosom joda. Razlikujemo dva tipa AIT; tip 1 je češći u bolesnika s podležećom tireoidnom patologijom, najčešće nodoznom strumom ili latentnom Gravesovom (Basedowljevom) bolešću, dok se tip 2 najčešće razvija u prethodno zdravoj štitnjači. AIH je znatno češća u bolesnika s otprije poznatim Hashimotovim tireoiditisom. Opisani su i miješani oblici bolesti. Bolesnike liječene amiodaronom potrebno je redovito pratiti, laboratorijski i klinički, kako bi se pravodobno otkrila bilo kakva odstupanja u tireoidnoj funkciji. Temelj liječenja AIH-a je nadomjesna terapija levotiroksinom. Često u tim slučajevima nije potrebno izostavljati amiodaron iz terapije. AIT tipa 1 liječi se tireostaticima, kao i ostale tireotoksikoze. Ako je moguće, preporuča se prekinuti podležeća amiodaronska terapija. Nasuprot AIT tipa 1, temeljni patofiziološki supstrat kojega je povećana sinteza i otpuštanje tireoidnih hormona, u AIT tipu 2 osnova je destruktivni tireoiditis uzrokovan amiodaronom, dezetilamiodaronom kao njegovim glavnim metabolitom i povećanim unosom joda. Osnova liječenja tog tipa bolesti je glukokortikoidna terapija.

Ključne riječi: *Amiodaron; Tireoidna disfunkcija; Amiodaronom izazvana hipotireoza; Amiodaronom izazvana tireotoksikoza*