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IODINE-INDUCED THYROID DISORDERS IN THE PRACTICE OF A CARDIOLOGIST

Oksana Makar[1], Nataliya Izhytska[1], Mar'yana Fedechko[1], Yaryna Leshchuk[1], Tomasz Kulpok-Baginski[2], Daniel Slezak[5], Klaudiusz Nadolny[3, 4], Jerzy Robert Ladny[3]

[1]Danylo Halytsky Lviv National Medical University
[2]Medical University of Silesia in Katowice, Faculty of Public Health, Institute of Public Health
[3]Department of Emergency Medicine and Disasters, Medical University of Bialystok
[4]Provincial Rescue Service in Katowice
[5]Faculty of Health Sciences with Subfaculty of Nursing and Institute of Maritime and Tropical Medicine, Departament of Emergency Medicine, Medical University of Gdansk

ABSTRACT

This article deals with the question of the influence of preparations that contain pharmacological doses of iodine on the functional activity of the thyroid gland. In the practice of a cardiologist amiodarone and x-ray contrasting substances are often used that may induce thyroid disorders in many ways, followed by hypothyroidism and thyrotoxicosis development.

KEY WORDS: iodine, thyroid dysfunction, amiodarone

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INTRODUCTION

The epidemiology of thyroid pathology is characterized by a unique feature which manifests itself, firstly, in the fact that it directly depends on the level of iodine intake in one population or another. Secondly, the thyroid gland is an organ that, due to unknown reasons so far, is more likely to develop autoimmune processes than others. Thus, iodine deficiency and autoimmune thyroidism are among the most common non-infectious human pathologies.

Due to the prevalence of drugs containing pharmacological doses of iodine (more than 1 mg per day) in clinical practice, it is relevant to study their effect on the functional activity of the thyroid gland. In the practice of the cardiologist such drugs comprise primarily amiodarone and iodine-containing X-ray contrast agents that are capable of inducing numerous thyroid disorders, with the subsequent development of both hypothyroidism and hyperthyroidism [2, 5, 7, 11, 13, 18, 22].

For cardiologists, the study of this issue is especially important, given the direct effect of the functional state of the thyroid gland on the cardiovascular system. It is known that one of the important complications of thyroid dysfunction, even at the subclinical stage, is an increase in morbidity and mortality of the population due to cardiac pathology [12, 25, 26]. According to the Rotterdam study, subclinical hypothyroidism is considered as independent of cholesterol, body mass index, smoking and β-blockers, and is a risk factor for atherosclerosis in the aorta and myocardial infarction in elderly women. It has been clearly demonstrated that the risk of developing aortic atherosclerosis increases by 1.7 times, and myocardial infarction by 2.3 times [15].

Some authors report a significantly higher risk of coronary heart disease and overall mortality among middle-aged and elderly men with latent hypothyroidism. As J.P. Walsh *et al.* (2005) described, ischemic heart disease among patients

ADDRESS FOR CORRESPONDENCE:
Oksana Makar, Department of Family Medicine, Lviv National Medical University, Pekarska St 69, 79000 Lviv, Ukraine; tel. (+38032) 2757632; e-mail kseni_kseni@ukr.net

with hypothyroidism is more likely to be found in comparison with euthyroid individuals (odds ratio 2.2, $p < 0.01$), with a significant association with coronary artery disease only in patients with TSH > 10 mU/l [31]. According to the same study, the probability of death and non-lethal coronary events was higher at subclinical (risk of 1.7; $p < 0.01$) and very high levels of manifested hypothyroidism (risk 2.6; $p < 0.01$). In this case, the frequency of myocardial infarction, congestive heart failure and the lethal consequences in patients with hypothyroidism is twice as high when compared with euthyroid individuals [14].

In elderly patients, thyrotoxicosis, which is associated with an increased heart rate and increased metabolic rate, can become a trigger factor in the manifestation of coronary heart disease or significantly impair coronary disease and, in some cases, may lead to the development of myocardial infarction [25, 32]. In this context, the increased mortality rate of patients with both subclinical and manifest thyrotoxicosis from cardiovascular diseases, in particular coronary heart disease when compared with euthyroid patients, has been repeatedly demonstrated [16, 28, 32]. After an ischemic heart disease, hyperthyroidism (including latent) is one of the most important causes of the occurrence of absolute cardiac arrhythmias, in particular, which was proven within the framework of the authoritative Framingham study [10]. This meta-analysis conducted showed that the risk of mortality in patients with subclinical thyrotoxicosis, including cardiovascular disease, was 41% higher than that of subjects with euthyroidism [14].

AMIODARONE AND IODINE-CONTAINING CONTRASTS

Amiodarone is a lipophilic substance, is a benzofuran derivative, characterized by a structural similarity to thyroxine and contains a significant proportion of iodine — about 75 mg of iodine in one tablet, of which about 9 mg enters the thyroid gland directly in the form of free particles. Such a large iodine load leads to a sharp increase in iodine levels in urine, which is sometimes stored up to 6 months after the drug is discontinued. The half-life of amiodarone lasts from 20 to 100 days [11]. Using iodine-containing X-ray contrast agents (by computer tomography or angiography) leads to the admission of about 13.5 mg of free iodine to the human body [20].

The frequency of thyroid dysfunction with prolonged use of amiodarone is 30–40%. The following have been distinguished as being among the mechanisms of the effect of amiodarone on the thyroid gland: inhibition of deiodinase types I and II; inhibition of the interaction of triiodothyronine with α- and β-receptors; the effect on the expression of the T3 receptor gene, adrenoreceptors, and myosin in the myocardium; and direct cytotoxic action on the thyroid gland [2, 6, 8, 17].

IODINE-INDUCED HYPOTHYROIDISM

Iodine-induced hypothyroidism usually develops in patients who are susceptible to the effects of inhibiting doses of iodine on the thyroid gland. Euthyroid individuals with chronic autoimmune thyroiditis, asymptomatic carriers of anti-thyroid antibodies, patients with subclinical hypothyroidism, along with patients who have had radioiodine therapy or subtotal resection of the thyroid gland in the past are particularly prone to the development of iodine-induced hypothyroidism [6, 11, 21]. One study demonstrated that the administration of excess iodine in patients with Hashimoto's thyroiditis caused hypothyroidism in 60% of cases [30]. Other studies have shown that hypothyroidism develops in almost 75% of euthyroid patients with anti-thyroid antibodies in long-term treatment with amiodarone [3].

According to the literature, this thyroid dysfunction is observed in 5–32% of patients taking amiodarone and is usually transient in patients without prior thyroid disease [6, 11, 30]. Although after the drug is discontinued the euthyroid condition is usually restored, it may take several months for this to happen due to the prolonged half-life period [21, 30]. According to the results of studies on the introduction of iodine-containing X-ray contrast agents during coronary angiography, this leads to the development of hypothyroidism in 3.5% of cases and the deterioration of its course in 12.3% [13].

Clinical manifestations of amiodarone-induced hypothyroidism may be transient or permanent, subclinical or manifested, their severity depending on the background state of the thyroid gland. In the presence of chronic autoimmune thyroiditis, persistent hypothyroidism usually develops. In this case, the development of hypothyroidism on the background of treatment with amiodarone is not accompanied by a decrease in its therapeutic effect. The withdrawal of the drug in some patients

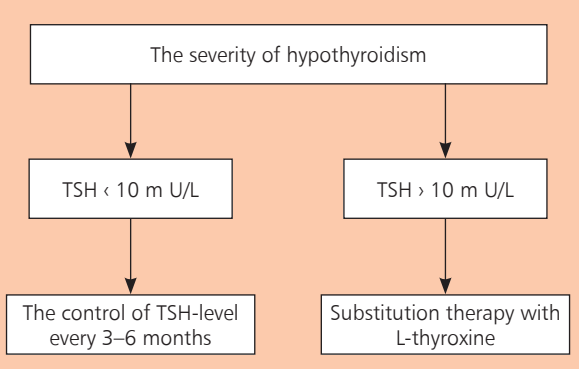

FIGURE 1. Medical tactics by amiodarone-induced hypothyroidism

may restore the euthyroid condition. Verification of amiodarone-induced hypothyroidism is not a contraindication to continuing treatment with amiodarone (Fig. 1). In the case of continued treatment, substitution therapy with L-thyroxine in small doses is prescribed until reaching the optimal target TSH level at the upper limit of the reference range [6, 11, 21, 30].

IODINE-INDUCED THYROTOXICOSIS

The basis of amiodarone-induced thyrotoxicosis is the excess synthesis and secretion of thyroid hormones — type 1, or the destruction of thyroid cells and the release of excess hormones in the blood — type 2 (Tab. 1) due to the effects of amiodarone on follicular thyroid cells [4, 27, 32]. Occasionally there are mixed forms. According to the results of studies, amiodarone-induced thyrotoxicosis develops in 12–20% of patients receiving this drug. In both cases, even after the cancellation of amiodarone, due to the long half-life of the drug, thyrotoxicosis may be sustained for a long time, sometimes up to 6 months [24, 32].

One of the earliest manifestations of amiodarone-induced thyrotoxicosis is the loss of the antiarrhythmic effect of amiodarone. The clinical picture is dominated by cardiovascular and mental disorders. There is an exacerbation of arrhythmias, the progression symptoms of coronary heart disease and heart failure. The risk of developing amiodarone-induced thyrotoxicosis does not depend on the cumulative dose of the drug, may develop unpredictably and in a sufficiently short time [1, 4, 11].

Iodine-induced thyrotoxicosis occurs after the administration of iodine-containing X-ray contrast agents in 0.1–1.2% of patients without concomitant thyroid disease. Instead, in patients with thyroid diseases, this happens much more often, namely in 5.2% of cases. As for the treatment of amiodarone and with the use of iodine-containing X-ray drugs, the risk factors are: advanced age, the presence of nodular goitre, lowered TSH and place of living in the iodine-deficient region [13].

Unlike amiodarone-induced hypothyroidism, treatment of iodine-induced thyrotoxicosis is more individual and differentiated. In patients with mild thyrotoxicosis, a small goitre and lack of background thyroid disease, it is sufficient to discontinue amiodarone. In patients with thyroid diseases, thyrotoxicosis usually does not disappear, even within a few months after discontinuation of the drug.

Treatment of amiodarone-induced thyrotoxicosis type 1 consists of the administration of high doses of thyreostatics (thiamazole 40–60 mg/day, carbimazole 60–90 mg/day, propylthiouracil 400––600 mg/day), as well as potassium perchlorate (600–1000 mg/day) and lithium (600–900 mg/day). In situations of the ineffectiveness of medication therapy, a thyroidectomy is conducted in some cases [9, 23, 29].

Table 1. Differences between amiodarone-induced thyrotoxicosis 1 and 2 type

Signs	AmIT 1 type	AmIT 2 type
Pathogenesis	Iodine-induced hyperthyroidism	Destructive thyroiditis
Background pathology of thyroid gland	Often	No
Goiter	Mostly multimodal goiter	Absent or small
Manifestation	Early (weeks)	Late (months)
Clinical course	Difficult	Medium-difficult
Dopplerography	High blood flow	Weakened blood flow
Thyroglobulin	Normal	High
Response to therapy	Unsatisfactory	Good
Development of hypothyroidism	No	Possible

In the treatment of amiodarone-induced type 2 thyrotoxicosis, the preference is given for glucocorticorticoids. The recommended starting dose is 1 mg/kg/day followed by a dose reduction every 2 weeks and a total duration of 3–5 months. Premature discontinuation of prednisolone is accompanied by a recurrence of thyrotoxicosis and the need for a renewal of treatment. In the case of the development of hypothyroidism, L-thyroxine is prescribed additionally [1, 9, 23].

The combination of amiodarone-induced thyrotoxicosis is based on combined therapy with thiothioamides (medium or high doses) and glucocorticoids (0.5 mg/kg/day). After normalizing the content of thyroid hormones, the dose of both drugs is gradually reduced, prednisolone being discontinued first. The duration of combination therapy is 3–5 months. In cases of resistance to medical treatment, or the presence of a background nodular goitre, surgical intervention on the thyroid gland is performed [2, 9, 23].

PRACTICAL RECOMMENDATIONS

Considering the widespread use of amiodarone and iodine-containing X-ray contrast agents in clinical practice, it is recommended to take into account the function and condition of the thyroid gland before their administration, in particular for the prevention of iodine-induced disorders. In particular, prior to the appointment of amiodarone or a procedure using iodine-containing X-ray drugs, it is recommended that the following examinations be performed: determination of TSH levels; thyroid peroxidase antibodies; and thyroid gland ultrasonography [2, 17].

Thus, it is possible to identify patients who are at high risk for the development of iodine-induced thyroid disease and to conduct their further observation, in order to correct anomalies in a timely manner. In the case of a patient with a node in the thyroid gland of a diameter greater than 1 cm found by ultrasonography, it is recommended to perform scintigraphy. In the treatment of amiodarone in the normal ascending functional state of the thyroid gland, it is recommended to conduct an examination 3 months after reaching the cumulative dose of the drug and subsequently every 6 months [11, 17].

CONCLUSIONS

Before prescribing amiodarone and procedures using iodine-containing X-ray diffraction agents, their effects on the thyroid gland should be taken into account. In order to identify patients at risk for the development of iodine-induced thyropathy, an examination of thyroid gland is recommended including determination of TSH levels, peroxidase antibodies, and ultrasonography. If these parameters are normal, it is recommended that they be monitored every 6 months during amiodarone treatment. In the case of iodine-induced thyroid disease, treatment is prescribed in accordance with the recommendations.

Conflict of interest: None declared.

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