Clinical case

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AMIODARONE-INDUCED THYROID DYSFUNCTION: CLINICAL CASE WITH LITERATURE REVIEW

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The article addresses the problem of amiodarone-induced thyroid dysfunction based in the clinical case. The literature data on the pathogenesis, diagnosis of this disease, as well as management tactics for different variants of amiodarone-associated thyroid dysfunction are shown.

KEY WORDS: amiodarone, thyroid dysfunction, diagnosis, treatment

АМІОДАРОН-ІНДУКОВАНА ДИСФУНКЦІЯ ЩИТОПОДІБНОЇ ЗАЛОЗИ: КЛІНІЧНИЙ ВИПАДОК З ОГЛЯДОМ ЛІТЕРАТУРИ

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На приладі клінічного випадка розглядається проблема дисфункції щитоподібної залози, що обумовлена прийомом аміодарону. Наведені дані літератури щодо патогенезу, діагностики цієї патології, а також щодо тактиці ведення хворих при різних варіантах аміодарон-індукованої дисфункції щитоподібної залози.

КЛЮЧОВІ СЛОВА: аміодарон, щитоподібна залоза, діагноз. лікування

АМИОДАРОН-ИНДУЦИРОВАННАЯ ДИСФУНКЦИЯ ЩИТОВИДНОЙ ЖЕЛЕЗЫ: КЛИНИЧЕСКИЙ СЛУЧАЙ С ОБЗОРОМ ЛИТЕРАТУРЫ

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На примере клинического случая рассматривается проблема дисфункции щитовидной железы, обусловленная приемом амиодарона. Приведены данные литературы по патогенез, диагностике этой патологии, а также по тактике ведения больных при различных вариантах амиодарон-индуцированной дисфункцией щитовидной железы.

КЛЮЧЕВЫЕ СЛОВА: амиодарон, щитовидная железа, диагностика, лечение

INTRODUCTION

Currently, the amiodarone has got the status the most commonly used antiarrhythmic drug in the world's clinical practice. In addition to its principle class III (potassium channel blockade) antiarrhythmic effects, amiodarone has class I (sodium channel blockade), class II (noncompetitive α- and β-blocking) and class IV (calcium channel activity) related actions [1].

Amiodarone's unique properties make it highly effective in the management of recurrent ventricular dysrhythmias, paroxysmal supraventricular dysrhythmias, including atrial fibrillation and flutter, and in the maintenance of sinus rhythm after electrical cardioversion of atrial fibrillation. Moreover, it has the added benefit of being well tolerated in patients with normal as well as impaired left ventricular systolic function [2].

Despite amiodarone's potent antidysrhythmic actions, its use is associated with numerous adverse effects on various organs, which are becoming more prevalent given the increasing incidence of dysrhythmias and wider amiodarone use. The common side effects include the thyroid gland dysfunction

(both hypo- and hyperfunction), which is due to amiodarone's high iodine content and its direct toxic effect on the thyroid gland [2].

In this article clinical case demonstrates diagnostic and treatment approaches to amiodarone-induced hypothyroidism on background of literature review.

CASE PRESENTATION

A 72-year-old man with a past medical history of non-Q-wave myocardial infarction, dyslipidemia and atrial fibrillation, but without previous history of thyroid gland disease has been followed-up in our clinic for 2 years. A year and a half ago patient developed episodes of atrial fibrillation confirmed on ECG Holter monitoring and amiodarone was initiated.

BACKGROUND

Amiodarone is a benzofuran derivative containing two atoms of iodine per molecule. A normal daily maintenance dose of amiodarone (200–400 mg) generates about 6–12 mg of free iodine per day. This results in an iodine load that far exceeds the World Health Organisation's recommended optimal iodine intake of 0.15–0.3 mg per day. In patients treated with amiodarone, urinary and plasma levels of inorganic iodide are found to increase up to 40-fold, whereas thyroidal iodide uptake and clearance decrease significantly [3–4] Amiodarone's effects on the thyroid gland are numerous and complex and occur via a number of differing mechanisms. These can be divided into iodine-induced effects and those due to the intrinsic properties of amiodarone [5]

Intrinsic amiodarone-related drug effects. Inhibition of monodeiodination (5-deiodinase activity) of T4 by amiodarone leads to a decrease in the generation of T3 from T4, a decrease in the clearance of reverse T3 (rT3) and consequently increased rT3 accumulation [6-7]. Amiodarone can lead to inhibition of T4 and T3 entry into the peripheral tissues. Both amiodarone and its principle metabolite desethylamiodarone (DEA) may have direct cytotoxic effects on the thyroid follicular cells, leading to a destructive thyroiditis [6, 8]. Furthermore, DEA is a noncompetitive inhibitor of the binding of thyroid hormone (T3) to the β1-thyroid hormone receptor (T3R) [6, 9].

Iodine-related effects of amiodarone on thyroid function. The normal autoregulation of iodine prevents normal individuals from becoming hyperthyroid after exposure to an iodine load. When intrathyroidal iodine concentrations reach a critical high level, iodine transport and thyroid hormone synthesis are transiently inhibited until intrathyroidal iodine stores return to normal levels (the Wolff-Chaikoff effect). Patients with underlying thyroid disease, however, have defects in autoregulation of iodine. This tends to occur in patients with underlying Hashimoto's disease [10]. In addition there may be iodine-related potentiation of thyroid autoimmunity and unregulated thyroid hormone synthesis in patients with underlying Graves' disease (Jod–Basedow effect) [10–11]. The risk of amiodarone-induced thyroid dysfunction depends on the presence of underlying thyroid disease. Thus, hypothyroidism develops more often in patients with underlying autoimmune thyroid disease, most likely as a result of the inability to escape from the Wolff-Chaikoff effect. Patients with multinodular goiter or subclinical Graves' disease tend to develop hyperthyroidism during treatment with amiodarone as a result of increased synthesis of thyroid hormones due to excess iodine from the amiodarone [12].

CASE PRESENTATION

Given the higher risk of developing amiodarone-induced thyroid dysfunction in the presence of underlying disorders our patient's thyroid function was evaluated prior to initiation of amiodarone therapy. Patient complaints were negative for dysfunction of thyroid gland. He denied muscle weakness, nervousness, any problems with defecation, difficulty sleeping or somnolence, body weigh changes, heat or cold intolerance, dysphagia and neck pain.

On physical examination the blood pressure was 112/78 mm Hg, heart rate=pulse=62 bpm, regular. Ocular reflexes were negative. Palpation revealed smooth, elastic, mobile, nontender thyroid gland of usual size. There were no discrete nodules appreciated and no bruits auscultated. There was no tremor. Lungs, heart, abdomen were unremarkable.

Thyroid function tests drawn before initiation of amiodarone treatment confirmed euthyroid patient's status: a thyroid stimulating hormone (TSH) was 2, 2 mIU/L (normal. 0,27–4,2 mIU/L), free thyroxin (T4) was 1.2 ng/dL (normal, 0,93–1,7 ng/dL), and

free triiodothyronine (T3) was 3,5 pg/mL (normal, 2,5–4,3 pg/mL), antithyroperoxidase (anti-TPO) and thyroglobulin antibody titers were low.

BACKGROUND

In iodine-sufficient areas, amiodarone-induced hypothyroidism is more common than hyperthyroidism, and may occur in up to 20 percent of patients treated with amiodarone [7]. In contrast, amiodarone-induced hyperthyroidism is more common than hypothyroidism in iodine-deficient regions [13]. The reported incidence of amiodarone-induced hypothyroidism varies widely, ranging from 6 % in countries with low iodine intake to 13 % in countries with a high dietary iodine intake. The risk of developing hypothyroidism is independent of the daily or cumulative dose of amiodarone [3]. The clinical manifestations and diagnosis of amiodarone-associated hypothyroidism are similar to those of hypothyroidism from any cause. Fatigue, lethargy, intolerance of cold, mental sluggishness and dry skin are commonly reported; goiter is uncommon.

Hypothyroidism and hypothyroid symptoms may develop as soon as two weeks or as late as 39 months after the initiation of amiodarone therapy [14]. Patients should have thyroid function assessed several weeks after starting amiodarone and every few months thereafter for the development of overt hypothyroidism, especially those with evidence for autoimmunity prior to initiating amiodarone [10, 15]. In general, patients should be monitored at 6 weeks and then every 3 months [3]. If equivocal biochemical results are obtained in clinically euthyroid patients, suggestive of subclinical hypothyroidism, then further testing in six weeks is recommended [16].

Hypothyroidism should be diagnosed on the basis of a screening serum TSH value before the patient has symptoms. Since small increases in serum TSH concentrations (10 to 20 mU/L) are seen in euthyroid patients for the first three to six months after amiodarone therapy is initiated, amiodarone-induced hypothyroidism should only be diagnosed when serum T4 concentrations are low-normal or low, or mild TSH elevation persists.

The alterations in thyroid function tests are usually divided into acute (≤ 3 months) and chronic (> 3 months) phases following the initiation of amiodarone therapy (see table) [17].

Table

Effects of amiodarone on thyroid function tests in euthyroid patients [17]

Thyroid hormone	Acute effects (≤ 3 months)	Chronic effects (> 3 months)
Total and free T4	↑ 50 %	Remains ↑ 20 – 40 % of baseline
T3	↓15 – 20 %, remains in low-normal range	Remains ↓20 %, remains in low-normal range
Reverse T3	↑ 200 %	Remains ↑150 %
TSH	↑20 – 50 %, transient, generally remains < 20 mU/L	Normal

CASE PRESENTATION

The patient was assigned a follow-up visit in 6 weeks of initiation of amiodarone therapy to assess its efficacy and safety. On follow-up visit patients still denied any complaints typical for hypo- or hyperfunction of thyroid gland. The laboratory tests showed signs of subclinical hypofunction of thyroid gland: TSH was 9, 7 mIU/L (0,27–4,2 mIU/L), free thyroxin (T4) was 1.22 ng/dL (0,93–-1,7 ng/dL), antithyroperoxidase (anti-TPO) and thyroglobulin antibody titers were still low.

BACKGROUND

There are two approaches to the treatment of autoimmune thyroiditisю. The first one means the discontinuation of amiodarone with replacing it with another antiarrhythmic drug. The second approach comprises normalization of thyroid function by replacement with T4 while amiodarone is continued. Discontinuation of amiodarone may not be feasible because of its highly effective anti-arrhythmic properties, especially in the treatment of life-threatening ventricular tachyarrhythmias.

That is why, a safer and more reliable option is to institute thyroid hormone replacement therapy, starting with 25–50 μg levothyroxine daily and increasing at intervals of 4–6 weeks until the symptoms have resolved and the target serum T4 level is achieved [3]. The goal of treatment is to restore the serum TSH concentration to normal and to bring serum thyroxine levels to the upper end of the normal range, as often seen in euthyroid patients who are receiving amiodarone [7]. It should take into account that a larger than usual dose may be required because of the likely effects of amiodarone on intrapituitary T4 metabolism and T3 production, and possibly thyroid hormone action [7]. It may be difficult to recognize the dysfunction because many changes in thyroid function test results occur in euthyroid patients who are receiving amiodarone and patients on amiodarone can have mildly elevated serum TSH levels despite adequate thyroid hormone replacement. Permanent hypothyroidism requiring T4 replacement is more common in patients with thyroid antibodies [18]. In such patients if TSH is raised, treatment with T4 should be started without delay [19].

On the other hand, overtreatment with levothyroxine may nullify the anti-arrhythmic effects of amiodarone, believed to be mediated via an intracellular state of hypothyroidism within the cardiac tissues [3].

The third opportunity to treat amiodarone-induced hypothyroidism is to restore the thyroid function with perchlorate. This approach was investigated in small studies, in which such treatment has been shown to restore normal thyroid function rapidly [20–21].

The drug relieves iodine-induced inhibition of thyroid hormone synthesis by its ability to discharge inorganic iodine and to block further entry of iodide into the thyroid [22]. But nowadays this approach cannot be generally recommended because of perchlorate toxicity which can result from either prolonged use or high dosages (> 1 g daily) and because hypothyroiddism can be easily and safely treated with thyroid hormone replacement [3].

In the absence of hypothyroid symptoms or thyroid antibodies, patients with moderately raised serum TSH (< 20 mU/l) but high-normal or raised serum free T4 concentrations may reflect amiodarone-induced alteration in thyroid function parameters or subclinical hypothyroidism [17].Close monitoring may be all that is necessary in these subjects [3].

Amiodarone is usually not discontinued unless it fails to control the underlying arrhythmia. However, if amiodarone is stopped, hypothyroidism in patients with no apparent preexisting thyroid disease often resolves. In contrast, hypothyroidism may persist after withdrawal of amiodarone in patients who have underlying chronic autoimmune thyroiditis with high titers of anti-TPO antibodies and goiter, and they therefore require permanent T4 therapy [17, 23].

CASE PRESENTATION

As our patient had no clinical symptoms of hypothyroidism and laboratory tests showed only moderately increased serum TSH and normal T4 level, the patient status was regarded as euthyroid and we decided to continue amiodarone therapy under close follow-up. Another argument in favor of expectant management tactics was the absence of thyroid antibodies before and during treatment with amiodarone. Patient was instructed to visit our clinic in 6 weeks for clinical check-up and laboratory tests evaluation. The follow-up confirmed the absence of clinical signs of thyroid gland dysfunction, laboratory tests showed the tendency of normalization of TSH, it was 6, 9 mIU/L versus 9, 7 mIU/L on previous visit (normal limits are 0,27–4,2 mIU/L). Three months later TSN returned to norm (4,1 mIU/L). Currently, the patient continues to receive amiodarone, and results of clinical and laboratory thyroid function tests remain normal.

CONCLUSIONS

Transient changes in thyroid function tests often occur in euthyroid individuals treated with amiodarone. Amiodarone causes predictable changes of tests that characterize the function of the thyroid gland, explicable in terms of physiological effects, caused by an iodine excess and its inhibition of deiodinase activity. Identify euthyroid hypothyroxinemia should not be considered as an indication for the abolition of amiodarone. While patients with pre-existing autoimmune thyroid disease (subclinical Hashimoto's thyroiditis or positive antithyroid antibodies) are at increased risk of developing amiodarone-induced hypothyroiddism, most patients remain euthyroid during amiodarone therapy. Since small increases in

serum TSH concentrations (10 to 20 mU/L) are seen in euthyroid patients for the first three to six months after amiodarone therapy is initiated, amiodarone-induced hypothyroidism should only be diagnosed when serum T4 concentrations are low-normal or low, or mild TSH elevation persists.

In most patients who develop amiodarone-induced hypothyroidism amiodarone therapy may be continued and euthyroidism should be restored by replacement with thyroid hormone in doses often larger than normal.

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