AMIODARONE-INDUCED THYROID DYSFUNCTION – CLINICAL PICTURE. STUDY ON 215 CASES

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AMIODARONE-INDUCED THYROID DYSFUNCTION – CLINICAL PICTURE STUDY ON 215 CASES (Abstract): Aim: The purpose of this study was to investigate the prevalence and the clinical-evolutionary implications of thyroid damage in patients treated with amiodarone in the Cardiology Clinic of the "Sf. Spiridon" University Hospital of Iasi. Material and Methods: The study included a group of 215 patients, 90 men and 125 women with ages between 35 and 87, hospitalized in the Cardiology Clinic between 2004 and 2014, who received amiodarone treatment, in most cases for the prophylaxis of various arrhythmias, both supra-ventricular and ventricular. Results: In 27.80% of the patients, the assessment of the thyroid function was imposed by the appearance of the clinical picture characteristic for hypothyroidism, and for 72.19% it was carried out as a routine examination. Amiodarone-induced hypothyroidism was clinically diagnosed in 20.85% of the patients. Hyperthyroidism occurring during treatment with Cordarone was found in 6.95% of the patients. The confirmation of the diagnosis of amiodarone-induced thyroid dysfunction was based on hormonal dosages (TSH, FT4 and even FT3 in some cases), on the endocrinological clinical consultation and on the imaging study – i.e. thyroid echography. Conclusions: Amiodarone-induced thyroid dysfunction is relatively rare compared to the number of patients treated with this anti-arrhythmic drug (27.8%) from the group under study. Thyroid dysfunction, regardless of the type (with hypo or hyper-function), represents a negative element in the evolution of patients with pre-existing heart diseases, not only by aggravating the clinical picture of the basic illness, but also by the necessity of permanently reviewing the therapeutic scheme imposed also by the association of thyroid dysfunction medication, according to case. Keywords: AMIODARONE, HYPOTHYROIDISM, HYPERTHYROIDISM.

Discovered in 1961 by Tondeur and Binon, amiodarone has been widely used especially in Europe, initially as anti-anginal preparation and later on as anti-arrhythmic, proving its effectiveness in the treatment of both atrial and ventricular arrhythmias with a malignant potential, being considered one the most effective anti-arrhythmic agents in preventing sudden arrhythmic cardiac death (1, 9). In 1985, amiodarone was approved by the FDA (Food and Drug Administration) for the treatment of atrial fibrillation and the prevention of recurrent ventricular tachy-
Despite this beneficial activity the prescription of amiodarone started to be limited due to the occurrence of serious side effects, some even disastrous, which were associated with the chronic use of the drug (2, 6, 8). Among these, the effects on the thyroid function raise the biggest issues for both patient and the physician; often it is necessary to reassess the therapeutic scheme because of the need to treat the newly occurred thyroid dysfunction. Thyroid abnormalities have been observed in 14-18% of the patients that received the minimum dose of amiodarone (8). The effects on the thyroid are variable:

- subclinical impairment, i.e. abnormal thyroid function detected only through regular laboratory tests (TSH, FT4, FT3) in the absence of any clinical manifestations (5, 6).

- clinically manifested thyroid dysfunction: amiodarone-induced thyrotoxicosis or hypothyroidism. Both can occur either on a previously normal thyroid gland or in the context of a pre-existing thyroid impairment, which they may worsen (3, 4, 6, 7, 8, 9).

The mechanisms of amiodarone activity on the thyroid are particularly complex: amiodarone inhibits the activity of deiodinase enzyme and thereby it decreases the peripheral conversion of thyroid hormones. It also decreases their renal elimination, increases T4, decreases T3 by about 25% and inhibits the entry of T4 and T3 in the peripheral tissues. (8). Amiodarone together with its metabolite, also has a direct cytotoxic effect on the thyroid follicular cells, the result being a destructive thyroiditis. It acts as a competitive antagonist of T3 at the heart level (3, 4, 7, 8, 9).

Amiodarone-induced thyroid impairment can resemble the clinical and biochemical picture of either hypothyroidism or hyperthyroidism. Amiodarone-induced hyperthyroidism may be of two types: Type I - due to excess iodine in amiodarone, which causes excessive synthesis of thyroid hormones; it usually occurs in subjects with prior thyroid impairment (subclinical or clinical) and Type 2 – it appears as an inflammatory process followed by the destruction in those with previously normal thyroid. The latter type is far more serious and it requires an urgent specific therapeutic protocol, which also involves the administration of glucocorticoids. Combined forms of thyroid impairment are rare (6, 8, 9). This study aimed to investigate the prevalence and the clinical-evolutionary implications of thyroid impairment in patients treated with amiodarone hospitalized in the Cardiology Clinic of the "St. Spiridon" University Hospital of Iași.

MATERIAL AND METHODS
The study included a group of 215 patients hospitalized in the Cardiology Clinic between 2004 and 2014, who received amiodarone treatment, in most cases for the prophylaxis of various arrhythmias, both supraventricular and ventricular. The group included 90 men and 125 women aged between 35 and 87. Patients were examined clinically and paraclinically (12-lead electrocardiogram, 2D echocardiography, M mode and Doppler, chest radiography, and laboratory data common in patients with heart disease: renal function and electrolytes, liver function, myocardial cytolysis enzymes). Since patients were going to receive amiodarone in the treatment scheme, the thyroid function was investigated for all of them, by routine hormone dosing (TSH, FT4, FT3) prior to the beginning of the treatment.
The basic pathology of the patients from the group was represented by the following conditions:
- acute viral myocarditis;
- acute myocardial infarction complicated by supraventricular arrhythmias and ventricular ESV and ventricular tachycardia;
- other forms of ischemic cardiopathy;
- ischemic dilatative and toxic (ethanolic) cardiomyopathy;
- HTA; on the background of this disease, the patients had different atrial arrhythmias (ESA, FA, atrial flutter) and ventricular arrhythmias (ESV), which were considered the expression of hypertensive cardiopathy;
- amiodarone administration pre-and post cardioversion.

RESULTS AND DISCUSSION

The indications for amiodarone administration in the study group were:
- controlling atrial and ventricular arrhythmias in the absence of or after the failure of other therapeutic alternatives;
- preparing for electrical cardioversion in patients with recent atrial fibrillation (onset under 1 year), with clear indication of cardioversion;
- the prophylaxis of atrial fibrillation recurrence after obtaining sinus rhythm;
- the prophylaxis and treatment of malignant ventricular rhythm disturbances occurred on the background of the coronary ischemic disease (i.e. IMA or other clinical forms of chronic ischemic cardiomyopathy);
- the prevention and treatment of severe ventricular rhythm disturbances occurred in the evolution of patients with dilative cardiomyopathy, having various aetiologies (ischemic, alcoholic, acute viral post myocarditis).

All patients in the group had their thyroid function investigated prior to the administration of amiodarone through TSH, FT4 and FT3 dosing, and it was within normal limits. The posology for amiodarone was, in most cases, as load - 800-1200 mg/day for 7-10 days, followed then by the maintenance dose 200 mg/day, 5-7 days/week (1 - 1.4 g/week). The duration of the treatment up to the moment of being included in the study (considered to be the moment that thyroid damage was discovered) was between 6 months and 8 years. The evaluation of the thyroid function, after starting the treatment, was made in 187 patients from the group (86.97%). In 52 patients (27.80%), the evaluation of the thyroid function was imposed by the appearance of the clinical picture characteristic for hypo- and hyperthyroidism; in the remaining 135 (72.19%) a routine examination was carried out. Amiodarone-induced hypothyroidism was clinically diagnosed in 39 patients (20.85%), of whom 13 were women and 26 men. Clinical elements suggestive for the hypothyroidism diagnosis were: somnolence, carotenodema, excessive bradycardia, important physical asthenia and skin infiltration. All cases were confirmed through elevated TSH values and low FT4 values.

Hyperthyroidism occurring during treatment with Cordarone has been encountered in 13 patients (6.95%), 10 men and 3 women. Hyperthyroidism apparition was suggested by the following signs and symptoms (classified as the hyperkinetic syndrome): sweating, tremor, the aggravation of a pre-existing atrial fibrillation by increasing the ventricular frequency that became refractory to all antiarrhythmic therapy, unexplainable weight loss and tachycardia. In 11 cases there was a wors-
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Focusing on the clinical picture of cardiac insufficiency. In all cases of hyperthyroidism, TSH values were lowered with normal or increased FT4. The confirmation of the amiodarone-induced thyroid dysfunction diagnosis of required collaboration with the endocrinologist, and it followed these steps:

1. Laboratory studies – i.e. TSH, FT4 and FT3 dosing in some situations. In case of amiodarone-induced hypothyroidism, laboratory data have objectified increased levels of TSH with low levels of free FT4 in all patients. Serum thyroglobulin was dosed to a limited number of patients and it had high values;

Patients with amiodarone-induced hyperthyroidism had high levels of free FT3 and FT4, and low, or even undetectable, levels of TSH;

2. Endocrinologic clinical examination;

3. Imaging studies – i.e. thyroid echography which, only in 5 patients with amiodarone-induced hypothyroidism, proved the enlargement of the thyroid and the nodular structure with hypoechogenic areas (partially orienting towards type 1 of amiodarone-induced thyroid dysfunction). In the remaining patients, thyroid echography was normal.

The current study revealed the following:

- None of the patients in the study presented clinically obvious thyroid impairment prior to the initiation of the amiodarone therapy;

- The occurrence of thyroid dysfunction induced by amiodarone did not correlate with the underlying heart pathology or the duration of the treatment, nor with other major cardiovascular risk factors. Some correlation was observed in the female group between hypothyroidism and obesity (85% of the women who developed amiodarone - induced hypothyroidisms were previously obese). The clinical picture corresponding to thyroid dysfunction had as a particular feature, according to the case, only the association with the signs of basic heart disease;

- The period of time between the initiation of the amiodarone treatment and the occurrence of clinical signs of thyroid dysfunction, was highly variable, i.e. between 6 months and 8 years. Also, no correlation could be established between the type of thyroid dysfunction (with hypo or hyperfunction) and the length of the treatment with amiodarone. In general, in female patients, thyroid dysfunction was diagnosed earlier because they came more often to the examination;

- There was no correlation between the administered amiodarone maintenance dose and the occurrence of a certain type of thyroid dysfunction;

- Amiodarone-induced hyperthyroidism was more common in male patients, on whom it caused an extremely unfavourable evolution and a prognosis: fibrillation and atrial flutter with rapid ventricular pace (over 150/min) resistant to antiarrhythmic therapy, and fatalities due to the worsening of the cardiac failure phenomena evolving up to cardiogenic shock and refractory acute renal failure.

Patients diagnosed with amiodarone-induced hypothyroidism had a somewhat favourable evolution after beginning the treatment with replacement hormones, i.e. alleviation of the clinical picture together with the correction of the thyroid hormone levels. Most patients who developed hypothyroidism showed an excessive bradycardia (i.e. 40-45/minute ventricular frequencies), symptoms (dizziness), which made
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them come to for examination.

CONCLUSIONS

Amiodarone-induced thyroid dysfunction is relatively rare compared to the high number of patients treated with this antiarrhythmic (27.8% of the studied group). Amiodarone-induced hypothyroidism is usually less obvious, in terms of the clinical picture, while the amiodarone-induced hyperthyroidism has a severe clinical picture by worsening the phenomena of cardiac insufficiency, by maintaining an elevated heart rate, generally resistant to antiarrhythmic drugs; some cases can be fatal especially when they occur on a severe basic cardiac pathology. Thyroid dysfunction, regardless of the type (with hypo- or hyper-function), represents a negative element in the evolution of the patients with pre-existing cardiac pathology, not only through the worsening of the clinical picture of the underlying disease, but also through the need to permanently review the therapeutic scheme also imposed by the association of the medication of the thyroid dysfunction, according to case.

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