THERAPEUTIC PARTICULARITIES IN AMIODARONE INDUCED THYROID DISORDER IN PATIENTS WITH UNDERLYING CARDIAC CONDITION

Irina Iuliana Costache¹, Voichiţa Mogos², Cristina Preda², Carmen Vulpoi², Maria-Christina Ungureanu²
University of Medicine and Pharmacy “Grigore T. Popa”- Iaşi
Faculty of Medicine
1. Department of Medical Specialties (I)
2. Department of Medical Specialties (II)

THERAPEUTIC PARTICULARITIES IN AMIODARONE INDUCED THYROID DISORDER IN PATIENTS WITH UNDERLYING CARDIAC CONDITION (Abstract). **Aim:** the analysis of therapeutic approach in patients with basic heart condition and amiodarone induced thyroid dysfunction – correlations with the evolution and prognosis. **Material and methods:** The study included 215 patients, 90 men and 125 women aged between 35 and 87, with different cardiac pathologies hospitalized in the Cardiology Clinic between 2004 -2014, who received amiodarone treatment, in most cases for prophylaxis of various arrhythmias, both supraventricular and ventricular. During the evolution, these patients have developed amiodarone-induced thyroid dysfunction (hypo- or hyperfunction). **Results and discussion:** The evaluation of thyroid function after starting treatment was performed in 187 patients (86.97%). Diagnosis of amiodarone-induced thyroid dysfunction was based on hormonal dosages of TSH, FT4 and FT3, endocrinological examination and thyroid ultrasound. Thyroid dysfunction treatment was initiated, depending on the situation, in all patients during the hospitalization. Treatment included anti thyroid drugs or hormones substitution and in some cases a minimal dose of prednisone. **Conclusions:** Thyroid dysfunction regardless of the type (with hypo- or hyper function) requires continuous changes of the cardiovascular treatment, and association, where appropriate, with thyroid dysfunction medication. In some cases the latter determines cardiovascular side effects, for instance corticotherapy may become a factor of imbalance for the hemodynamic status of the patient (by fluid retention, increased blood pressure, hyper glycemia). **Keywords:** AMIODARONE, THYROID HORMONES, ANTI THYROID DRUGS

Amiodarone is a class III anti arrhythmic drug (according to the classification of Vaughan Williams) which is effective in the treatment and prophylaxis of arrhythmias, supra ventricular and ventricular (especially those that are life-threatening) (1). Apparently, it presents structural similarities with the thyroxin hormone produced and released by the thyroid gland (1, 2, 3, 4, 8). Thyroid abnormalities were observed in 14-18% of patients receiving the low dose of amiodarone (1, 2, 3, 8). Thyroid effects are variable: abnormal thyroid function tests detected only by
periodic laboratory control (TSH, FT4, FT3) in the absence of any clinical manifestations or thyroid clinical dysfunction: amiodarone-induced thyrotoxicosis form, or hypothyroidism. Both can occur on a previously normal thyroid gland or in the context of a pre-existing thyroid impairment that may worsen (2, 3, 4, 5, 8, 9).

Mechanism of amiodarone activity on thyroid hormones levels is particularly complex: Amiodarone inhibits 5'-deiodinase and thereby decreases the peripheral conversion of T4 in T3. Their renal elimination also decreases, T4 level increase and T3 decrease by about 25%. T4 and T3 entry in peripheral tissues is also inhibited. T4 levels increase by 40% in the first 1-4 months of treatment with amiodarone (10, 11, 12). An inhibition of the pituitary deiodinase can be seen after 3 months of treatment and leads to higher levels of thyroid stimulating hormone (TSH). Amiodarone, together with its metabolite, also have 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 cardiac level (3, 4, 6, 7, 8, 9, 13, 14, 15).

Amiodarone-induced thyroid impairment (AIT) can resemble the clinical and biochemical picture of either hypothyroidism or hyperthyroidism. Amiodarone-induced hyperthyroidism may be of two types: Type 1 AIT occurs in patients with an underlying thyroid pathology such as autonomous nodular goiter or Graves’ disease - in these patients, there is accelerated thyroid hormone synthesis secondary to the iodide load from the amiodarone therapy (the Jod-Basedow phenomenon) (15); Type 2 - appears as a destructive inflammatory process followed by destruction in patients with a previously normal thyroid. It is a destructive thyroiditis with preformed hormones releasing from the damaged thyroid follicular cells (10, 11, 13, 14, 15). This type of development requires specific therapeutic management that involves the administration of glucocorticoids. Combined forms of thyroid impairment are rare (10, 11, 12, 13, 15). The thyrotoxic phase may last several weeks to several months, and it is often followed by a hypothyroid phase with eventual recovery in most patients. For unclear reasons, the toxic effects of amiodarone may take two to three years to manifest (10, 11).

This study analyzes the therapeutic particularities in amiodarone-induced thyroid dysfunction in patients with severe underlying heart disease in order to improve long-term prognosis.

MATERIAL AND METHODS

The study included 215 patients hospitalized in the Cardiology Clinic of “Sf. Spiridon” Hospital Iasi between 2004-2014, who received amiodarone treatment, mostly for prophylaxis of various arrhythmias, both supraventricular and ventricular. The group included 90 (41.86%) men and 125 (58.13%) women aged between 35 and 87 (fig. 1).

![Fig. 1. Gender distribution of patients](image)

Basic cardiac pathology of the study group included: acute viral myocarditis - 2 (0.93%) cases, acute myocardial infarction -16(7.44%) complicated with supraventricular arrhythmias (atrial extra-systoles, paroxysmal atrial fibrillation), systematized ventricular extra-systolas (bi, trigeminy) and ventricular tachycardia, other forms of...
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ischemic heart disease – 11 (5.11%) cases, ischemic dilated and toxic cardiomyopathy - 49 (22.79%) cases, hypertension - 76 (35.34%) cases complicated with atrial and ventricular arrhythmias (fig 2). In 60 patients (27.9%) it was performed electrical cardioversion to convert atrial fibrillation to sinus rhythm and amiodarone was administered pre- and post-cardioversion using a standard protocol.

Patients were assessed clinically (heart auscultation, assessing signs of cardiac decompensation) and laboratory (12-lead electrocardiogram, echocardiography 2D, M mode and Doppler, chest radiography and laboratory data common in patients with heart disease: renal function and electrolytes, liver function, cardiac enzymes). Since patients were going to receive amiodarone in the treatment regimen, thyroid function was investigated for all by dosing routine hormone (TSH, FT4, FT3) prior to treatment.

RESULTS AND DISCUSSION
The administration of amiodarone was mostly in the load form - 800-1200 mg/day for 7-10 days followed by maintenance dose 200 mg (1 tablet/day 5-7 days/week (1 -1.4 g/week). In some patients the initial administration was intravenous, within 24 hours, because a rapid action was required.

Duration of treatment until the time of discovery of thyroid damage was between 6 months and 8 years. In all patients the thyroid function was investigated prior to the administration of amiodarone (TSH, FT4 and FT3 levels that were within normal limits). Evaluation of thyroid function after starting treatment occurred in 187 (86.97%) patients. Diagnosis of amiodarone-induced thyroid dysfunction was based on laboratory data – i.e. dosing TSH, FT4 and FT3.

Amiodarone-induced hypothyroidism has been diagnosed clinically in 39 (20.85%) patients and confirmed by elevated levels of TSH and low levels of FT4. Thyrotoxicosis occurred during Amiodarone treatment in 13 (6.95%) patients (fig 3). In all cases of thyrotoxicosis TSH level was low with FT4 normal or increased. 2 patients presented undetectable TSH values with FT4 and FT3 greatly increased (in one case with FT4 100 IU/ml). In 7 patients with thyrotoxicosis ultrasound showed a hypervascularization of thyroid (thyrotoxicosis type 1) and in 6 cases the vascularization was decreased or absent (thyrotoxicosis type 2). Thyroid ultrasound was abnormal only in 16 patients with amiodarone-induced hypothyroidism: enlargement of the thyroid, hypoechochogenic areas. In the remaining patients, the thyroid ultrasound investigation was not performed.
All patients with amiodarone-induced thyroid dysfunction were monitored initially in hospital for a period depending on the particularities of each case (between one week and one month). Thyroid dysfunction treatment was initiated, if necessary, in the hospital.

The first evaluation was performed after one month, and at 3, 6 and 12 months afterwards and consisted of clinical examination, electrocardiogram, echocardiogram, TSH and FT4, FT3 determination. In patients receiving Methimazole, monthly blood counts were indicated. Also, in patients receiving prednisone, the blood glucose and lipid profile were monitored. The patients were evaluated than annually.

For patients who confirmed the diagnosis of hypothyroidism we still maintained amiodarone in the treatment plan and we associated Levothyroxine in gradually increasing doses (25 µg/day 7 days, than 50 µg/day, up to one month after the patient was assessed once again). One month evaluation revealed: normalization of TSH and FT4 (all patients) and normalization of the thyroid ultrasound aspect. Evaluation at 3 and 6 months showed normal levels of thyroid hormones; we continued the initial dose of Levothyroxine. All patients maintained normal thyroid function at 12 months under a minimum dose of Levothyroxine. No patient required a dose more than 50 µg/day.

For patients diagnosed with amiodarone-induced thyrotoxicosis it was necessary to replace amiodarone with another anti arrhythmic drug and start treatment with Methimazole (doses between 10-40 mg/day) or/plus prednisone. The evolution of these patients was unpredictable; in 25 % of cases, after a variable period of time (3 to 6 months) they developed hypothyroidism (TSH greatly increased) which imposed a temporary elimination of anti thyroid drugs. After a short period of hypothyroidism (3 months), 3 patients presented thyrotoxicosis relapse, which led to the resuming of treatment with anti thyroid drugs. Only one patient in this group needed thyroidectomy.

Amiodarone-induced thyrotoxicosis was more common in male patients, which presented an evolution and a very unfavorable prognosis: 2 patients had atrial fibrillation and atrial flutter with rapid ventricular rate (over 150/min ) resistant to anti arrhythmic treatment, and another two patients died due to worsening heart failure phenomena evolving to cardiogenic shock and refractory acute renal failure.

Patients diagnosed with amiodarone-induced hypothyroidism had a somewhat favorable evolution after hormone replacement. Levothyroxine therapy improved the clinical picture of hypothyroidism in all patients without requiring discontinuation of amiodarone in any of the cases.
The side effects related to the medication of thyroid dysfunction in the study group were the following:
- 3 patients (one male and two females) had moderate leucopenia (between 2,800-3,400/mm³) that could be related to the treatment with Methimazole - no therapeutic intervention was required;
- In the group of patients treated with Levothyroxine no major adverse effects were observed, only in 5 cases heart rate increased, unjustified by any other situation;
- In two patients (one male and one female) who received the combination of Methimazole and prednisone high blood glucose levels were observed between 2 weeks and 2 months after the initiation of corticotherapy, but not exceeding 150 mg/dl; one of the patients presented as well high values of blood pressure.

**CONCLUSIONS**
Amiodarone-induced thyroid dysfunction requires immediate therapy. Our study showed that hypothyroidism amiodarone-induced generally had a better prognosis after hormone replacement therapy and did not require removal of anti arrhythmic regimen, thyroid dysfunction in this case being solved only by the introduction of thyroid hormone replacement therapy.

However, Amiodarone-induced thyrotoxicosis proved to be a severe clinical presentation, worsening heart failure by maintaining a high heart rate, generally resistant to anti arrhythmic drugs; it usually required the removal of amiodarone treatment and anti thyroid drugs; in all cases the evolution was slow and unpredictable, sometimes being fatal. Two patients had atrial fibrillation and atrial flutter with rapid ventricular rate (over 150/min) resistant to anti arrhythmic treatment, and another two patients died due to worsening heart failure. We consider thyroid dysfunction (either hypothyroidism or thyrotoxicosis) a negative element in the evolution of patients with pre-existing heart disease, not only by clinical worsening of the underlying disease, but also by the need to permanently review the cardiovascular treatment and the possible association with appropriate medication to the thyroid dysfunction. It is also necessary to consider the side effects of thyroid dysfunction medication, including corticosteroid treatment.

**REFERENCES**
THE UTILITY OF LIPOPOLYSACCHARIDE-BINDING PROTEIN IN THE DIFFERENTIATION BETWEEN PERIPROSTHETIC JOINT INFECTION AND ASEPTIC LOOSENING?

The pre-operative differentiation between periprosthetic joint infection (PJI) and aseptic loosening after total hip (THA) or knee (TKA) arthroplasty is essential for successful therapy and relies in part on the use of molecular markers. A recent prospective, controlled, clinical trial study conducted by Friedrich MJ and collaborators assessed serum levels of lipopolysaccharide-binding protein (LBP) from one hundred and twenty patients presenting with a painful TKA or TKA with indication for surgical revision. Pre-operative blood and serum samples were collected and analysed also for white blood cell (WBC) count and C-reactive protein (CRP). The definite diagnosis of periprosthetic joint infection was determined on the basis of clinical, microbiological and histopathological examination. LBP showed significantly higher values in PJI compared with aseptic loosening (p < 0.001) and control (p < 0.001), with a specificity of 66 % and a sensitivity of 71 % at a cutoff value of >7 ng/ml. In combination with CRP, the positive predictive value for PJI was at 0.67; negative predictive value with both negative was at 0.77. The authors concluded that the use of LBP in serum appears not to be a more accurate marker than CRP level in serum for detecting PJI, and on the basis of these results, they cannot recommend the sole use of LBP for differentiating PJI and aseptic loosening following THA and TKA. (Friedrich MJ, Randau TM, Wimmer MD et al. Lipopolysaccharide-binding protein: A valuable biomarker in the differentiation between periprosthetic joint infection and aseptic loosening? Int Orthop. 2014 May 15. [Epub ahead of print]. PMID: 24827968).