Review Article

Amiodarone therapy: don't forget thyroid

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Abstract

Amiodarone is an effective anti-arrhythmic agent for control of various life threatening ventricular tachyarrhythmias but may give various side effects. Clinically relevant thyroid dysfunction is not uncommon during amiodarone therapy and is caused by iodide excess and inhibition of deiodinase activity. Amiodarone induced thyroid dysfunction varies from asymptomatic variation in thyroid function to clinically overt hypothyroidism and thyrotoxicosis. Prolonged elimination and half life and associated complications warrant for rational prescribing and long term follow up.

Keywords: Amiodarone, Thyroid disorder, Wolff-Chaikoff effect, Hypothyroidism, thyrotoxicosis.

Introduction

Amiodarone is a type III anti-arrhythmic agent used for treatment of various arrhythmias like paroxysmal atrial fibrillation to ventricular tachycardia in patients with structural heart disease or congestive heart failure.[1]

Amiodarone is a benzofuran derivative and its molecule is structurally similar to thyroxin (T4) and contains 2 atoms of iodine per molecule[2] which amounts to 37% iodine by weight (i.e. each 200 mg tablet contains about 75 mg of Iodine) of which approximately 10% is released as free iodine after deiodination. This results in an iodine load that far exceeds the World Health Organization'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]

Amiodarone (with its active metabolite, desethylamiodarone formed in the liver) blocks the potassium channel which slows repolarization, causing an increase in the duration of the action potential and in the refractoriness of cardiac tissue; this has the effect of prolonging the QT interval. It also blocks sodium channels (at rapid heart rate) and calcium channels too. It is also a relatively potent noncompetitive alpha-blocker and beta-blocker but has no clinically significant negative inotropic effect.[1] Amiodarone is a highly lipophilic compound with a delayed onset of action (an interval of 2 to 3 days) and a long elimination half-life (up to 6 months).[4] However, one must be aware of associated several side-effects, including photosensitivity, corneal microdeposits, pulmonary fibrosis, hepatotoxicity, peripheral neuropathy, hyperthyroidism and hypothyroidism.[5]

Amiodarone and Thyroid:

The incidence of amiodarone-induced thyroid dysfunction ranges from 14% to 18% and is related to environmental iodine adequacy versus iodine deficiency.[6] Amiodarone has many effects on thyroid hormone synthesis and their peripheral metabolism (mainly in liver and brain). This leads to abnormal results on thyroid function studies without overt dysfunction (in > 50% cases) to symptomatic thyrotoxicosis or hypothyroidism. Signs and symptoms of alteration in thyroid function take longer to develop than do changes in serum levels of thyroid hormones. Occasionally, amiodarone can also cause goiter without apparent thyroid dysfunction.[7] During amiodarone metabolism in liver, large amount of iodide is released which initiates the Wolff-Chaikoff effect (blockage of thyroid iodide uptake and hormone synthesis as an adaptive response to high concentration of iodide to avoid hyperthyroidism).[8] However, continuous influx of iodide leads to resumption of normal thyroid hormone synthesis and protects patient from developing hypothyroidism due to sustained Wolf-Chaikoff effect.[9]

Amiodarone is a strong inhibitor of type-I 5'-monodeiodinase in peripheral tissue predominantly thyroid and liver (major extrathyroidal Tri-iodothyronine, [T3] production site) resulting in reduced conversion of T4 to T3 and also reduces the clearance of T4 and reverse T3 (rT3).[10] Consequently, the serum levels Free T4 (FT4), T4 and rT3 increase and T3 decreases by 20-25%. Inhibition of type-II 5'-deiodinase activity results in reduced intrapituitary T3 concentration and causes a rise in serum TSH level.[11] Amiodarone also inhibits the entry of thyroid hormones into peripheral tissue (mainly liver) and increases T4 and reduces T3 production. Furthermore, desethylamiodarone (active metabolite of amiodarone) act as a competitive inhibitor of T3 at cardiac cellular level.

Thyroid Hormones During Amiodarone Treatment:

Alterations in the circulating thyroid hormones levels occur within days after the start of treatment with amiodarone with ongoing changes during the course of therapy. Serum total T4, rT3 (up to 20%) and FT4 levels increase within 24 hours of amiodarone treatment and T4 levels can increase by as much as 40% at 1-4 months of treatment. This increase is an expected finding and does not in itself denote hyperthyroidism[2] and then gradually falls towards high normal level. Due to reduced conversion of T4 to T3, serum T3 levels are typically at the lower end of the normal reference range (up to 30% within first few weeks) and continue to be low despite continued amiodarone therapy. TSH levels vary in response to amiodarone. Shortly after therapy is started, TSH

Table-1: Amiodarone and thyroid hormones in euthyroid individuals (incidence >50%).

Parameter	Effect	Cause
T4 / FT4	Increases up to 40% of baseline within 1-4 months and gradually falls towards high normal level afterward.	Inhibition of type-I 5'-monodeiodinase in peripheral tissue predominantly thyroid and liver (major extrathyroidal Tri-iodothyronine, [T3] production site) resulting in reduced conversion of T4 to T3 and also reduces the clearance of T4 and reverse T3 (rT3)
rT3	Increases up to 20% of baseline within 1-4 months and gradually falls towards high normal level afterward	
T3	Reduces up to 30% of baseline within 1-4 months and continued to be at lower normal limit afterward.	
TSH	Increases shortly after treatment and returns to normal limits in 3 months.	Inhibition of type-II 5'-deiodinase activity results in reduced intrapituitary T3 concentration and causes a rise in serum TSH level.
	In few cases with continued treatment, level may fall below normal limit as well.	Partial T3 agonist effect.

levels increase because of the initial suppression of the thyroid hormones and the reduced negative feedback. With continuing amiodarone therapy (more than 3 months) TSH levels often return to normal.[2] In some cases with prolonged treatment with amiodarone, a low TSH level may be observed suggesting a partial T3 agonist effect[10,11] (Table-1).

Amiodarone Induced Thyrotoxicosis (AIT):

Amiodarone induced thyrotoxicosis is more prevalent in iodine-depleted areas (about 10%) while in iodine-repleted areas such as the United Kingdom and United States, about 3% of users become thyrotoxic and risk increases with increased dosage.[12] However, in a Dutch study involving euthyroid subjects living in an area with a moderately sufficient intake of iodine, the incidence of AIT was twice that of AIH (amiodarone induced hypothyroidism).[13] It predominantly occurs in men (male to female ration 3:1)[6] and may develop any time during amiodarone therapy or even several months after discontinuation due to long elimination half life of amiodarone.

Pathogenesis:

Two forms of AIT have been described. Type 1 (AIT-1) usually affects patients with latent or preexisting thyroid disorders and is more common in areas of low iodine intake. It is caused by iodine-induced excess thyroid hormone synthesis and release (Jod-Basedow phenomenon). Type 2 (AIT-2) is found in patients with a previously normal thyroid gland and is caused by a direct cytotoxic effect of amiodarone and its metabolites on thyroid follicular cells. This results in destructive thyroiditis and release of preformed or stored thyroid hormones into circulation. However, mixed forms of AIT may occur in an abnormal thyroid gland, with features of thyroiditis and iodine excess (Jod-Basedow phenomenon).

Clinical Presentation:

AIT should be suspected in a patient who was previously stable on amiodarone but develops tremors, sweating, weight loss or showing signs of cardiac decompensation or onset of new arrhythmia. However, patients may lack cardiac manifestations of thyrotoxicosis because of amiodarone's intrinsic inhibitory effects on the heart (similar to the actions of beta adrenergic blockers and calcium channel blockers). Patients with AIT-1 usually have a known goiter (diffuse or multinodular) while patients with AIT-2 may have tender mildly enlarged thyroid gland.

Diagnosis:

It is important to distinguish between two types as specific treatments exist for both types, and choosing the wrong therapy results in ineffective or delayed responses and exposes patients to unjustifiable drug side effects. However, existence of mixed form poses a diagnostic challenge.

Diagnosis of thyrotoxicosis is made by a marked increase in serum levels of FT4 (or high total T4 and FT4 index), with a markedly suppressed serum TSH level. Serum T3 levels in such individuals may be either elevated or normal; the presentation of T4 toxicosis being one of the peculiar features of AIT. Although differentiation between the two forms of AIT may not always be feasible, this can be made by following tools:

a) Radioiodine Uptake Study: In AIT-1 cases, 24-hour uptake is usually normal-to-high and low to suppress in AIT-2.[14]

b) Radionuclide Thyroid Scan (Tc-99m pertechnetate /Iodine-123): shows good tracer uptake of radiotracer in AIT-1 and low to markedly reduced (depending upon the phase of thyroiditis) in AIT-2.

c) Serum Interleukin-6 (IL-6) levels: it is a promising tool for discrimination as it is markedly elevated in AIT-2 but normal to marginally raised in AIT-1. However, this is not widely available.[15]

d) Colour Doppler Sonography: is considered a good tool for rapid differentiation between the two types of AIT. It shows parenchymal blood flow in AIT-1 patients while flow is reduced to absent in AIT-2.

Treatment:

Is difficult and requires differentiation between types of AIT as it is different for both groups. It is important to know that thyrotoxicosis may not reverse for months because of the drug's long elimination half-life and the large total-body iodine stores. Unless amiodarone is ineffective in controlling the arrhythmia, it is usually continued while treating amiodarone induced thyrotoxicosis.

In patients with mild thyrotoxicosis and a normal underlying thyroid gland or a small goitre, the hyperthyroid state often resolves rapidly after amiodarone is withdrawn. In patients with thyrotoxicosis and underlying gland abnormality, in addition to withdrawal of amiodarone, definitive treatment includes the use of thionamides, perchlorate, radio-iodine therapy, plasmapharesis, and surgery.

High doses of thionamides (e.g. carbimazole or methimazole 40-60 mg/day, or propylthiouracil 100-150 mg qid) are required to block thyroid hormone synthesis as these are less effective in the presence of high intrathyroidal iodide concentrations. If thyrotoxicosis is severe or inadequately treated with thionamides, potassium perchlorate (starting with 250 mg 6 hourly, tapered off and stopped after 4-6 weeks) can be added for effective control. Perchlorate competitively blocks iodide from entering the thyroid by an effect on the Na+/I symporter, but it has no effect on the iodination process itself. It is concentrated by the thyroid

tissue in a manner similar to iodide but is not significantly metabolised in the gland or peripherally. Long-term use of perchlorate is not advocated because of its association with fatal aplastic anaemia.[2]

Radioactive iodine-131 (I-131) therapy is generally not effective in treating patients with AIT, because of hypersaturated iodine pool prevents sufficient thyroidal uptake of the I-131.[10] However, in iodine depleted areas, this may be an effective option.[16] Under circumstances in which patients fail to improve with medical therapy and discontinuation of amiodarone is impractical, a total or near-total thyroidectomy may be more appropriate provided patients withstand surgical stress.[2] Plasmapheresis has occasionally been tried, although not always successfully, to ameliorate severe thyrotoxicosis refractory to medical therapy.[17]

AIT-2 is treated with a relatively long course of a glucocorticoid for its anti-inflammatory and membrane-stabilizing effects.[18] Prednisone 30 to 40 mg daily, tapered over 2 to 3 months, is recommended. Lithium, which inhibits thyroid hormone secretion, has been tried with good results in a relatively small number of patients with presumptive AIT-2[19] (Table-2).

Amiodarone Induced Hypothyroidism (AIH):

It is more prevalent in iodine replete areas (13%) than iodine depleted regions (6%)[9] and is independent of the daily or cumulative dose of amiodarone. Elderly and female users are at higher risk probably due to higher prevalence of underlying thyroid abnormality. The relative risk of developing AIH was found to be 13-fold higher in female patients with positive thyroid antibodies, as compared with men without thyroid antibodies.[13] AIH may be transient or persistent; the latter is almost always associated with an underlying thyroid disorder. Unlike thyrotoxicosis, which may occur anytime during therapy or even after discontinuation of therapy, hypothyroidism is usually an early event and it is uncommon after the first 18 months of amiodarone treatment.[13]

Pathogenesis:

Failure of thyroid to escape from the Wolff-Chaikoff effect induced by large amount of iodide is the possible explanation of AIH. Thyroid hormone biosynthesis is impaired because of the persistent block in intrathyroidal iodine organification as evident by the positive perchlorate discharge test in patients with AIH.[14] This may arise from an underlying thyroid abnormality like autoimmune thyroiditis and suggests that iodide excess could unmask some pre-existent subclinical thyroid disease to produce overt thyroid failure.[9]

Clinical Presentation:

Similar to spontaneous hypothyroidism, AIH often is associated with vague symptoms. Fatigue, weight gain, constipation, dyspnoea and cold intolerance are the usual symptoms. Patients may have bradycardia, diastolic hypertension, dry skin, brittle nails or sluggish reflexes. Goiter is rarely associated with hypothyroidism.[20]

Diagnosis:

Thyroid profile shows raised TSH (>20 mU/l) with low T4 and FT4 titers in the serum. Serum T3 concentration is an unreliable indicator as it can be low in euthyroid patients, whereas hypothyroid patients may have T3 levels within the normal range. In 40%of patients, thyroid antibodies are positive in serum.[9]

Radioactive iodine uptake study and thyroid scan show inappropriately elevated thyroid radiotracer uptake in spite of large iodine load.[14]

Treatment:

Hypothyroidism in patients with no preexisting thyroid disease often resolves after discontinuation of amiodarone therapy. However, in patients with pre-existing autoimmune thyroiditis, hypothyroidism may persist after discontinuation of amiodarone. If discontinuation of amiodarone is not possible due to life threatening ventricular tachyarrhythmia, thyroid

Table-2: Comparison of Type-I and Type- II Amiodarone Induced Thyrotoxicosis.

Parameter	AIT Type-I	AIT Type-II
Pre-existing thyroid disorder	Yes	No
Iodine Depleted Area	Common	Less Common
Etiology	Jod- Basedow Phenomenon	Destructive Thyroiditis
Thyroid Gland	Diffuse / Nodular enlargement	Tender and mildly enlarged
Radioiodine Uptake	Normal to High	Low to Suppressed
Tc-99m Thyroid Scan	Good uptake	Markedly reduced
Interleukin-6	Normal or marginally high	Markedly elevated
Doppler Ultrasound	Increased flow	Reduced flow
Treatment	Stop amiodarone, High Dose ATD, Potassium Perchlorate, I-131 in iodine depleted area, Thyroidectomy	Stop Amiodarone, Steroid for membrane stabilization, Lithium to reduced hormone release.

hormone replacement therapy may be instituted. The initial dosage of levothyroxine (drug of choice) is 25 to 50 µg/day and increasing at intervals of 4-6 weeks until symptoms have resolved with serum T4 level in upper normal range. Larger doses of T4 are required to offset the inhibitory effects of amiodarone on the conversion of T4 to T3. However, over treatment must be avoided as it may undermine the anti-arrhythmic effect of amiodarone (Figure).

Normalization of thyroid function may be delayed due to prolonged elimination life of amiodarone and also due to

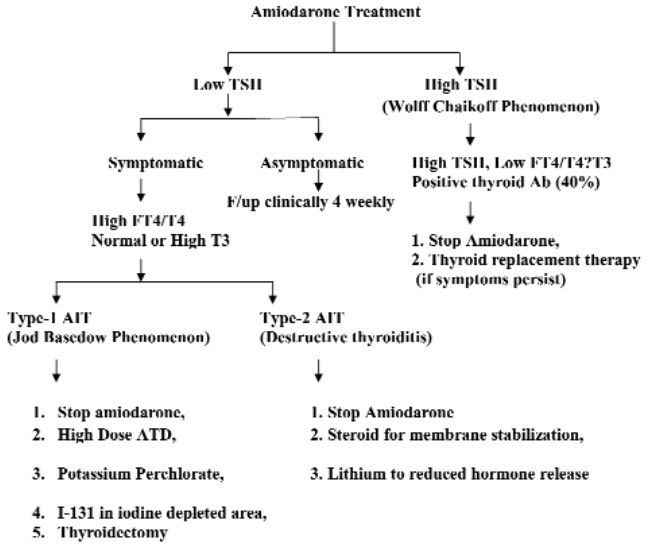

Figure: Algorithm showing management of amiodarone induced thyroid disorders.

pre-existing autoimmune thyroid disorder. For hasty recovery, a short course (10- 30 days) of treatment with potassium perchlorate (0.75-1 g/d) may be given. Potassium perchlorate inhibits thyroidal uptake of iodide and minimizes the inhibitory effect of intrathyroidal iodine content. Long-term use of perchlorate is not advocated because of its association with fatal aplastic anaemia.[2]

Conclusion

Amiodarone is an effective anti-arrhythmic agent for control of various life threatening ventricular tachyarrhythmias but may give various side effects. Clinically relevant thyroid dysfunction is not uncommon during amiodarone therapy and is caused by iodide excess and inhibition of deiodinase activity. Amiodarone induced thyroid dysfunction varies from asymptomatic variation in thyroid function to clinically overt hypothyroidism and thyrotoxicosis. Prolonged elimination half life and associated complications warrant for rational prescribing and long term follow up.

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