CLINICAL VIGNETTE

Amiodarone Induced Thyroiditis

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The patient is an 81-year-old woman with a history of congestive heart failure, atrial fibrillation, hypertension, and hypercholesterolemia. She had a cardiac defibrillator placement for systolic congestive heart failure and VT. Medications included carvedilol, amiodarone, isosorbide, furosemide, warfarin, and valsartan. On routine follow-up with EP, interrogation of her pacer showed VT episodes 1-2x/month, without atrial fibrillation. Follow-up interrogation one month later showed more VT episodes that resolved spontaneously. She was asymptomatic. She has been on amiodarone 200 mg daily for several years and tolerated it well. Due to her VT episodes, her dosing was increased to 200 mg alternating with 400 mg daily.

One month after her dose increase, she noted shortness of breath, fatigue, and palpitations after traveling with increased salt from eating at restaurants. She reported a 10 pound weight loss over the past year due to decreased appetite, increasing palpitations, and shortness of breath for several days, which prompted her admission. She denied tremors, sweats, and hot flashes. She has chronic loose stools for years, attributed to her medications. Physical exam revealed normal blood pressure, heart rate, and oxygen saturation. Her thyroid was not enlarged; she had crackles on lung exam. Cardiac exam revealed normal rate and rhythm. She had no tremors or proptosis. CT angiogram of the chest was negative for pulmonary embolus. Monitoring showed VT episodes lasting as long as 30 seconds, confirmed on ICD interrogation. Labs showed suppressed TSH, elevated FT4, normal TSI, normal TBI immunoglobulin, and high TBO antibody. Prior thyroid function tests have all been normal, including several months prior. Ultrasound of her thyroid showed borderline thyromegaly. She had elevated LFTs with no biliary obstruction or suspicious liver lesions noted on ultrasound imaging. Her prior LFTs from several months previously were normal. Due to the elevation of her LFTs, her statin was discontinued.

She was started on methimazole 20 mg daily and prednisone 40 mg daily for likely amiodarone induced hyperthyroidism. Her amiodarone was discontinued, and she started sotalol for arrhythmia control. The patient was on methimazole for 3 months but had further elevation of liver enzymes prompting discontinuation. She remained stable on prednisone. Both her LFTs and TFTs improved on prednisone, which was titrated off after 9 months. Her TSH has remained stable off medications.

Thyroid Hormone Metabolism

Thyroid hormone production requires iodine. About 60-80 ug of iodine is needed to maintain daily hormone production. The thyroid gland generally has 5,000 to 10,000 ug of iodine stored as a reserve. The iodide is transported and joined with tyrosine to make T4 and T3. Some of the T4 is eventually deiodinated to T3 and released.[1]

Amiodarone and the Thyroid

Amiodarone is an iodinated benzofuran derivative drug that is used in the treatment of ventricular arrhythmias, paroxysmal atrial tachycardia, atrial fibrillation, and maintenance of sinus rhythm after cardioversion of atrial fibrillation. Side effects include photosensitivity, corneal microdeposits, pulmonary toxicity, hepatotoxicity, peripheral neuropathy, and thyroid disorders including hyperthyroidism and hypothyroidism.[2] Amiodarone has 2 iodine atoms that are released after metabolism in the liver. The amount of iodine in a 100 mg dose of amiodarone is about 3 mg of free iodine. The typical American diet has about 0.15 mg to 0.3 mg/day of iodine. Amiodarone is lipophilic and accumulates in adipose tissue, cardiac skeletal muscle, and thyroid. The half-life is about 100 days. [3]

Amiodarone can affect the thyroid due to effect of amiodarone itself as well as the effect of the iodine load. Effects on the thyroid include inhibition of outer ring deiodination of thyroxine T4, resulting in decrease of T3 production. The metabolite of amiodarone blocks T3 receptor binding to nuclear receptors and decreases expression of thyroid hormone related genes. Amiodarone can also affect thyroid follicular cells resulting in destructive thyroiditis.[3]

In the first 3 months of starting amiodarone therapy, generally T3 decreases and T4, FT4, reverse T3, and TSH increase. After 3 months of therapy, TSH usually returns to normal, while T4, FT4, and rT3 remain at the upper end of normal or slightly elevated. T3 is low or low normal.[3]

Amiodarone induced hypothyroidism is more common in areas of sufficient iodine intake; the prevalence of amiodarone-induced hypothyroidism can be as high as 22%. It usually occurs within the first 6-12 months of amiodarone therapy.[3]

T4 replacement can be used to restore the serum TSH and amiodarone treatment can be continued unless it fails to treat the arrhythmia. When amiodarone is discontinued,

hypothyroidism can resolve in patients with no preexisting thyroid disease. However in patients with underlying autoimmune thyroiditis, the hypothyroidism may persist.[3]
Amiodarone induced thyrotoxicosis (AIT) has a lower prevalence than hypothyroidism and can occur at any time during treatment. There are 2 types, and it is important to distinguish them for therapeutic management. However, differentiating the types can be challenging. Symptoms of hyperthyroidism may be masked due to the beta blocking activity of amiodarone and interference of binding T3 to its nuclear receptor by amiodarone metabolites. Common symptoms include recurrent arrhythmias, heart failure, weight loss, low grade fever, and restlessness.[4]

Type 1 amiodarone-induced thyrotoxicosis develops in patients who have a pre-existing thyroid disorder such as Graves' disease or multinodular goiter. Thyrotoxicosis occurs due to the high iodine load in amiodarone, leading to a high thyroid hormone production.[2]

Type 2 amiodarone-induced thyrotoxicosis results from amiodarone causing a subacute thyroiditis with release of thyroid hormones in the circulation.[5]

Diagnosis

Iodine 131 uptake can differentiate type 1 from 2. The uptake is high in type 1; in type 2, there is little to no uptake due to destruction or damage of the thyroid. In some patients with type 1, however, the uptake can be low due to high intrathyroidal iodine concentrations from amiodarone. This is common in iodine sufficient areas and can lead to misdiagnosis.[6]

Interleukin 6 can be normal to mildly elevated in type 1 AIT and very elevated in type 2. IL6 can be used to follow patients with type 2 during treatment.

Color flow doppler sonography is thought to be the best test to distinguish between type 1 and 2 AIT. The test determines blood flow in the thyroid, and 80% of patients can be classified as having type 1 or 2.[7] 99mtc sestamibi thyroid uptake and scintigraphy is also used.[8]

Treatment

Amiodarone has beta adrenergic effects, and it has a long half-life of about 100 days. Therefore, the effect of withdrawing the medication would not be immediately effective. In cases of ventricular arrhythmias, consideration should be given to continuing the amiodarone. For non-life threatening ventricular arrhythmias, alternative antiarrhythmics can be used.

Treatment of type 1 thyrotoxicosis includes use of thionamide (methimazole 30-40 mg or PTU 450 mg to 600 mg daily). The dose is eventually tapered to a low maintenance dose. If amiodarone is stopped, the length of thionamide treatment can take 6-18 months. If amiodarone is continued, the thionamide should be continued.[4]

If the radioiodine uptake is high, I 131 ablation can allow amiodarone to be restarted for control of recurrent arrhythmia.[9]

For patients who are refractory to antithyroid drug therapy, thyroidectomy is recommended.[10]

In type 2 AIT, prednisone at 40-60 mg daily is used and tapered over the next 2-3 months. Lithium can also be used because it inhibits thyroid hormone secretion.[4]

In some patients, it can be difficult to distinguish between type 1 or 2 AIT and prednisone and methimazole are both used for treatment.

Monitoring

For patients starting amiodarone, thyroid function tests are checked at baseline the monitored every 3-4 months during treatment. Since thyroid dysfunction can occur after amiodarone is stopped, monitoring should continue for about 1 year after discontinuation of the drug.[2]

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