Study of Thyroid Dysfunction among Patient with Amiodarone Therapy in Government Stanley Hospital

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Abstract: Background: Amiodarone is a potent antiarrhythmic drug that is used to treat ventricular and supraventricular tachyarrhythmias. Clinically relevant thyroid dysfunction is not uncommon during amiodarone therapy, and requires careful diagnosis and treatment. Materials and Methods: We conducted study in the Government Stanley Hospital among the patient attending cardiology OPD. Around 200 subjects were included in this study. All the patients are investigated for thyroid profile and other blood tests and detailed history recorded based on the standard proforma. Results: Thyroid dysfunction occurs in about 27 % of 200 patients who took amiodarone in our study. 10 % patients has subclinical hypothyroidism, 2 % has clinical hypothyroidism, 6 % has subclinical thyrotoxicosis, 9 % has clinical thyrotoxicosis. Conclusion: Thyroid dysfunction is very common in our part of country; since our geographical area is mixed with iodine deficient and iodine sufficient population, it is very important to do thyroid function test among patient undergoing chronic Amiodarone Therapy; still larger studies are needed in this area as it is first study in our population, to become it generalised.

Keywords: AIT (Amiodarone Induced Thyrotoxicosis), AIH (Amiodarone Induced Hypothyroidism), TSH, FT4, FT3, Amiodarone and Thyroid

1. Background

Clinically relevant Thyroid dysfunction is most common in patients taking Amiodarone. It ranges through a wide spectrum ranging from subclinical hypothyroidism to clinical thyrotoxicosis. The Thyroid dysfunction that happens with Amiodarone is explained in physiological terms due to iodide excess and inhibition of deiodinase activity⁷.

First included in 1974, Amiodarone is a Vaughan William’s Class III anti-arrhythmic drug used to treat ventricular and supra-ventricular arrhythmias. It is a benzofuran derivative, iodine rich compound with structural similarity to thyroxine. Amiodarone also causes an anti-thyroid action⁵, via Wolff–Chaîkoff effect, due its large amount of iodine in its molecule, which causes a particular "cardiac hypothyroidism" with bradycardia and arrhythmia. The effects of amiodarone on thyroid function can be divided into those effects that are intrinsic properties⁴ of the drug and those effects that are due to iodine.

Aim

1) To find out the prevalence of Thyroid dysfunction among patient undergoing amiodarone therapy.
2) To find out the associated risk factors with Thyroid dysfunction among patient undergoing Amiodarone therapy.

2. Materials and Methods

The study was a descriptive, cross sectional study conducted on 200 patients attending cardiology OP in Government Stanley Medical College Hospital. The study was conducted for a period of 3 months from Jan 2019 to May 2019.

For every case selected, informed written consent was obtained prior to the commencement of the study. A detailed clinical history, symptoms and signs of Hypothyroidism, details of the drugs taken including Amiodarone dosage, other drugs taken, indication for which those drugs prescribed, associated co morbidity illnesses like Diabetes Mellitus, Systemic Hypertension, Hyperlipidemia, Bronchial Asthma, duration and other cardiac drugs or any Chronic Kidney disease pre-existing Thyroid disease, family History of Diabetes Mellitus, Hypertension ,Thyroid Illness, geographical area from which patient residing, Dietary history including Iodine intake and results of routine investigations like Complete Blood count, Electrocardiography, Echocardiogram, X-ray chest – PA view, Renal function test, Liver Function Test (SGOT/ SGPT), Urine Routine examination, Blood sugar (Random, Fasting and Post pyramidal – when indicated) will be prospectively recorded in the semi-structured Performa. Also in all cases, blood for Thyroid Profile, TSH, FT3, and FT4 will be taken by performing venepuncture and estimation was done at Clinical Biochemical Laboratory, Biochemical Department at Government Stanley Medical College, Chennai. Risk Factor statistically analysed with Chi-square test, Test of significance is done by p value. Prevalence will be given by Percentage.

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Inclusion Criteria
All patients with heart disease on treatment with amiodarone therapy for more than 3 months are included in the study.

Exclusion Criteria
1) Patient on Amiodarone treatment for less than 3 months.
2) Patient on Amiodarone treatment for life threatening illness like Myocardial infarction.
3) Patients with sinus nodal bradycardia.
4) Patients with second or third degree heart block with no artificial pacemaker.
5) Patients with compromised lung function.
6) Patients with compromised renal function.
7) Patients not consenting to be a part of the study.
8) Patients experiencing any form of allergic reactions to amiodarone.
9) Pregnant women or women expecting pregnancy.
10) Lactating mothers.
11) Patients complaining any form of toxicity to amiodarone.
12) Patients with deranged liver function tests.
13) Patients already on thyroxine supplementation.
14) Patients on antithyroid drugs.
15) Patients with prior history of thyroid surgery.
16) Patients with history of sepsis, trauma (that warranted hospitalization)

3. Results and Interpretation
Our study among 200 cardiac patients in this study showed a significant thyroid dysfunction in wide range of spectrum. Of the 200 patients, 108 were males and 92 were females, selected after using inclusion and exclusion criteria. 93 subjects were using iodised salt and 107 were using de-iodised salt. Of patients using amiodarone, 200 mg were taken by 141 patients; 300 mg by 46 subjects and 400 mg by 13 subjects. Among 200 subjects, Diabetes was present in 46 subjects, Hypertension in 26 subjects, both in 13 subjects. No co-morbidities were seen in 115 patients. Hypothyroidism is more common in female sex, whereas hyperthyroidism occurs almost equally in both sexes in our study.

Age is not a significant risk factor in the development of thyroid dysfunction although predominant subjects with hypothyroidism occur in 40-60 years and predominant subjects with hyperthyroidism occurs in 20-60 years.

With reference to the presenting ailment or the symptomatology in patients, palpitation was present in 5 subjects (2.5%); weight loss was seen in 4 subjects (2%). Dyspnea present in 9 subjects (4.5%), lethargy in 4 subjects (2%) and no symptoms in 178 subjects (89%).

Among the 200 patients we enrolled, 93 out of 200 subjects were using iodized salt comes to around 46.5% and 107 out of 200 subjects were using de-iodized salt that accounts to 53.5%.

Of the 200 patients, Sub-clinical hypothyroidism was found in 19 subjects (10%). Clinical hypothyroidism in 5 subjects (2%), Thyrotoxicosis found in 17 subjects (9%) and subclinical thyrotoxicosis present in 13 subjects (6%). 146 subjects were found to be normal in this study. In our study all the patient with hypothyroidism were started on levothyroxine treatment and all hyperthyroidism were started on antithyroid drugs.

The overall incidence of Amiodarone induced Thyrotoxicosis was ranging from 1 to 23% and Amiodarone induced Hypothyroidism was ranging from 1% to 32% in various studies as against 27% reported in our study.

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4. Discussion

Amiodarone is an important anti-arrhythmic drug used for treating atrial as well as ventricular arrhythmias. It is an iodine containing drug and its mechanism of action interferes with the iodine uptake and inhibition of de-iodinase activity. Hence the chance of occurrence of both hypothyroidism and hyperthyroidism is very high with the intake of Amiodarone for cardiac diseases. Amiodarone chemically resembles thyroxine (thyroid hormone), and its binding to the nuclear thyroid receptor might contribute to some of its pharmacologic and toxic actions.

Amiodarone, when given chronically at a 200 mg day-dose, releases 5-10 mg of iodide into the circulation. The drug is accumulated in almost all tissues5, including the thyroid. After withdrawal, it may take months until the excess of iodine is cleared, because of a terminal elimination half-life of amiodarone estimated at 8-107 days. Numerous inhibitory mechanisms protect the organism from an excessive production of thyroid hormones. Iodine inhibits its organification5 (the so-called Wolff Chaikoff effect) as well as the thyroid clearance of iodide: however, when the absolute uptake of iodide is considered, a three-fold increase is observed after 6 weeks of treatment by amiodarone. While in normal conditions of iodine delivery, no free iodide can be detected in the thyroid, in amiodarone-treated patients, the trapped iodide is built-up in the gland, presumably because its organic binding becomes the rate-limiting step of intra-thyroidal iodine metabolism. Amiodarone slows conduction rate and prolongs the refractory period of the SA and AV nodes. It also prolongs the refractory periods of the ventricles, bundles of His, and the Purkinje fibers without exhibiting any effects on the conduction rate. Amiodarone has been shown to prolong the myocardial cell action potential duration and refractory period and is a non-competitive β-adrenergic inhibitor. It also shows beta blocker-like and calcium channel blocker-like actions on the SA and AV nodes, increases the refractory period via sodium- and potassium-channel effects, and slows intra-cardiac conduction of the cardiac action potential, via sodium-channel effects. It is suggested that amiodarone may also exacerbate the phenotype associated with Long QT-3 syndrome causing mutations such as AKPQ. This effect is due to a combination of blocking the peak sodium current, but also contributing to increased persistent sodium current.

Amiodarone is extensively metabolized in the liver by cytochrome P450 3A4 and can affect the metabolism of numerous other drugs. It interacts with digoxin, warfarin, phenytoin, and others. The major metabolite of amiodarone is desethylamiodarone (DEA), which also has antiarrhythmic properties. The metabolism of amiodarone is inhibited by grapefruit juice, leading to elevated serum levels of amiodarone.

Thyroid hormones are catabolic hormones which are known to play essential roles in various metabolic processes. Altered thyroid states have been reported to be associated with metabolic disorders as well as cardiovascular diseases. Hypothyroidism has been reported to impair cardiac contractility, decreased cardiac output, increased vascular resistance, reduced chronotropy, cardiac atrophy, and cardiac failure. The effect of hypothyroidism on cardiac function is linked with attendant dyslipidaemia and atherosclerosis. On the other hand, hyperthyroidism-induced cardiovascular dysfunction is due to the hyper metabolic state and accelerated free radical production in the mitochondria with resultant changes in the antioxidant defense system caused by high levels of thyroid hormones.

Amiodarone induced thyrotoxicosis5 occurs predominantly in low iodine intake individual. Diabetes Mellitus when coexist with Amiodarone treated patients, thyroid dysfunction is more common. Thyroid dysfunction is common among supra ventricular tachyarrhythmia with amiodarone compared to ventricular tachyarrhythmia with amiodarone. As Amiodarone dosage increases the chance of thyroid dysfunction increases.

As dosage of Amiodarone increases, so does the chance of thyroid dysfunction. The occurrence of Hypothyroidism is high when the duration of Amiodarone intake is less than 15 months and Hyperthyroidism is high, when the duration of intake is more than 15 months. Hypothyroidism is more common in females and the occurrence of hyperthyroidism is equal in both sexes. Amiodarone induced hypothyroidism can be treated easily with hormonal substitution. Hyperthyroidism is more challenging. There exist two forms of amiodarone-induced Hyperthyroidism5 (AIT): AIT type 1 is directly related to the iodine compound of amiodarone and responds to thyrostatic therapy. Type 2 is a consequence of the direct toxicity of amiodarone to the thyroid gland and is treated primarily with glucocorticoids6.

Amiodarone is very lipophilic and is concentrated in adipose tissue, cardiac and skeletal muscle, and the thyroid. Elimination from the body occurs with a half-life of approximately 100 days. Amiodarone toxicity can therefore occur well after drug withdrawal.

5. Conclusion and Future Recommendations

Thyroid dysfunction is very common in our part of country; since our geographical area is mixed with iodine deficient
and iodine sufficient population, it is therefore necessary to do thyroid function tests for all patients who are planned to be on therapy for more than 3 months. Still larger studies are needed in this area, as there are very few study in our population in this regard and so the results need to be generalised after Large scale Studies.

6. Conflict of Interest: Nil

7. Grants: Nil

References