Review

# A clinicopathological review of amiodarone-induced thyroid disorders

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Certain drugs could disturb physiological function and anatomical structure of thyroid gland and; to some instance, the peripheral thyroid hormone metabolism as part of their adverse reactions. In fact, commonly prescribed drugs including anti-convulsants, non-steroidal anti-inflammatory drugs, Beta-adrenoceptor antagonists, steroid hormones and heparin may produce an abnormal thyroid function test, albeit an absence of detected clinical features for thyroid dysfunction. Therefore, it is recommended to undertake a routine monitoring of thyroid function test, both at baseline and every 3 to 6 months thereafter, in vulnerable individuals (for example, those with thyroid antibodies or euthyroid goiter) receiving such medication.

## INTRODUCTION

Certain drugs could disturb physiological function and anatomical structure of thyroid gland and; to some instance, the peripheral thyroid hormone metabolism as part of their adverse reactions. These drugs have an ability to influence tests utilized to investigate thyroid function through alterations in the synthesis, transport and / or metabolism of thyroid hormones, as well as their main impact on thyroid stimulating hormone (TSH) synthesis and secretion. However, few drugs could result in important changes in clinical thyroid state, but difficulty in interpretation of thyroid function tests often observed.

In fact, commonly prescribed drugs including anti-convulsants, non-steroidal anti-inflammatory drugs, Beta-adrenoceptor antagonists, steroid hormones and heparin may produce an abnormal thyroid function test, albeit an absence of detected clinical features for thyroid dysfunction. In contrast, lithium and iodine containing drugs, such as radiographic contrast agents and amiodarone, may result sometimes in overt thyroid disease.[1]

In general, drugs affect the thyroid gland in different ways and on several aspects, so there are medicines that interfere with thyroid function testing like Dopamine agonists, drugs that cause displacement of thyroid hormones from thyroid–binding globulin like nonsteroidal anti-inflammatory drugs,[2] in addition to medications that prevent conversion of T4 to T3 for example Amiodarone and iodinated contrast media which can inhibit the conversion of $T_4$ to $T_3$ both in the peripheral circulation and in the pituitary gland, making a confused thyroid function abnormalities.[3] Drugs may also affect T4 requirements such as serotonin reuptake inhibitors.

Previously, In nine patients getting thyroxine remedy, an elevation in thyrotropin levels and a reduction in $FT_4$ levels were distinguished after the addition of sertraline hydrochloride.[4] in addition to a aforementioned groups and examples of drugs, several well documented drugs produce significant thyroid dysfunction with identifiable pathological changes, to this group iodides, iodide-containing preparations like amidarone, lithium, and interferon alfa treatment belongs.[1, 5-7] The following discussion will try to highlight those changes affecting thyroid glands anatomy and

physiology due to treatment by Amidarone. Therefore, it is recommended to undertake a routine monitoring of thyroid function test, both at baseline and every 3 to 6 months thereafter, in vulnerable individuals (for example, those with thyroid antibodies or euthyroid goiter) receiving such medication.[3]

## PHARMACOLOGY OF AMIDARONE

Amiodarone is regarded as a potent antiarrhythmic drug which is mainly given for those patients suffering from ventricular and supraventricular tachyarrhythmias. This compound is a benzofuran-derived, enrich with iodine and the structural similarity with thyroxine (T4) is also observed. It is known that Amiodarone contains iodine approximately 37% by weight. Each 200-mg tablet is ordinary comprised about 75 mg of organic iodide, 8-17% of which is yield as free iodide. Standard maintenance therapy by means of 200 mg amiodarone can supply to some extent greater than 100 times the daily iodine requirement. Furthermore, its intensive level found in various tissues and organs namely adipose tissue, muscle, liver, lung, and thyroid gland as it is highly lipid-soluble.[8]

The elimination half-life of amiodarone is highly variable. In one study it was 52.6 ± 23.7 (±sd) days,[9] while in another 40 ± 10 days,[10] and still higher for its metabolite desethylamiodarone (DEA). These results explain why after its withdrawal, the drug and its metabolites remain available for several months.

## AMIODARONE VSERSUS THYROID GLAND

In up to 14-18% of patients receipting long-term amiodarone therapy, thyroid gland defects have been distinguished. However, several studies proposed that with the lower doses of amiodarone (150-330 mg) incidence of thyroid dysfunction is just 3.7%. Such effects range from abnormal thyroid function test findings to clinically significant thyroid dysfunction, which may be either amiodarone-induced thyrotoxicosis (AIT) or amiodarone-induced hypothyroidism (AIH).[11, 12] Both can develop in apparently normal thyroid glands or even in glands with preexisting abnormalities.

As illustrated in table 1, Amiodarone has many effects on thyroid physiology, histology as well as the peripheral metabolism of thyroid hormones. These outcomes are also detected in amiodarone-treated patients who remain euthyroid, and are largely explicable in terms of the physiological effects of iodide excess and inhibition of 5'-deiodinase activity. More than 50% of patients who take long-term amiodarone treatment display abnormal results on thyroid function test, and the majority persist clinically euthyroid. Occasionally, amiodarone can also cause thyroid enlargement without evident thyroid dysfunction.[13]

The large amount of released iodide during the metabolism of amiodarone leads to a protective blockage of additional thyroidal iodide uptake and prevents increased thyroid hormone biosynthesis, the phenomenon so-called Wolff-Chaikoff effect.[14] impairment in thyroid hormone biosynthesis is eminent because of the persistent block in intrathyroidal iodine organification, as manifest by the positive perchlorate discharge test in patients with AIH.[15] As many as 40% of patients who develop hypothyroidism after amiodarone administration have detectable serum thyroid antibodies, suggesting that excess of iodide could expose some pre-existent subclinical thyroid disease to produce overt thyroid failure.[16] Although the majority of patients treated with amiodarone remain euthyroid, some develop thyroid dysfunction, *i.e*., thyrotoxicosis and hypothyroidism.[17]

**Table 1.** Summary of selected actions, onset and effects of amiodarone imply on pathophysiology and histology of thyroid gland.

| Action | Effect | Onset and duration |
|---|---|---|
| **Inhibition of type I 5'-deiodinase enzyme activity** | Serum levels of T4 and rT3 increase and the serum levels of T3 decrease by 20-25%. | 2 weeks after institution of amiodarone therapy |
| **Inhibition of type II 5'-deiodinase enzyme activity in the pituitary gland** | Increase in thyroid-stimulating hormone (TSH) level | Seen in the first 1-3 months and return to normal in 2-3 months |
| **Inhibition of entry of T4 and T3 into the peripheral tissue** | Serum T4 levels increase by an average of 40% above pretreatment level | After 1-4 months of treatment with amiodarone |
| **Increase thyroidal iodine intake due to high drug-iodine content** | Increase hormone synthesis | 3 to 8 weeks after an increase in iodide supplementation |
| **Direct cytotoxic effect on the thyroid follicular cells** | destructive thyroiditis | Associated with prolonged drug treatment |

Amiodarone-induced thyrotoxicosis (AIT) is seems to be occurred more frequently in geographical areas with low iodine intake, whereas AIH is more common in iodine-sufficient areas.[18, 19] AIT may occur, usually suddenly and explosively, early or after several years of amiodarone

usage.[20] Two forms of AIT have been distinct. Type 1 usually affects patients with latent or preexisting thyroid disorders and is more common in areas of deficient iodine intake. It is caused by iodine-induced excess thyroid hormone synthesis and release (Jod-Basedow phenomenon). Type 2 takes place in those people with a previously normal thyroid gland and is caused by a destructive thyroiditis that leads to the release of preformed thyroid hormones from the damaged thyroid follicles. Moreover, mixed forms of AIT may exist in an abnormal thyroid gland, with features of destructive processes and iodine excess. AIH happens more commonly than AIT in iodine-sufficient regions.[16] In contrast to AIT, AIH is slightly more frequent in women, with a female to male ratio of 1.5:1.[18, 20] Furthermore, AIH patients are older than AIT patients,[21] and usually the former develops earlier than the latter, both in patients with seemingly normal thyroid glands and in patients with preexisting thyroid disorders.[15,20] The most likely mechanisms of underlying AIH are an improved vulnerability to the inhibitory consequence of iodine on thyroid hormone synthesis along with an incapability of the thyroid gland to escape from the acute Wolff-Chaikoff effect after an iodine load in patients with preexisting Hashimoto thyroiditis. In addition, destructive thyroiditis might hasten the natural trend of Hashimoto thyroiditis toward hypothyroidism. Patients without preexisting thyroid abnormalities are assumed to have subtle defects in iodine organification that may lead to reduced thyroid hormone synthesis, down regulation of peripheral thyroid hormone receptors, and consequent exhibited hypothyroidism occurrence.[22]

A biopsy of the thyroid gland is unnecessary in most patients. Recently, the histological changes that occur with amiodarone administration have been studied in a research setting,[23] in animals like rats, also in several human cases treated with this drug.

In a histological study to evaluate the influence of Amiodarone on thyroid follicular cells in Albino rat; light microscopical observations of thyroid gland treated with amiodarone exhibited changes ranged from normal pictures to irregular thyroid follicles with disrupted lining epithelium and marked cellular infiltration between follicles. Electron microscopic examination showed irregular nuclei with chromatin condensation, dilatation of Rough Endoplasmic Reticulum, increased lysosomes numbers and intra-lysosomal inclusion bodies with vesiculation of cytoplasm. Addition of carbimazole only; as treatment; reflected partial improvement, while both carbimazole and prednisolone showed marked improvement nearly for all the thyroid specimens.[23]

Other report, for a patient with AIT with toxic thyroid effects, verified three main pathological findings by electron microscopy in a fine-needle aspiration biopsy. These pathological discoveries were: multilamellar lysosomal inclusions, intramitchondrial glycogen inclusions: both ultrastructural findings indicating damage to thyroid follicular cells, and a microscopic morphological pattern of thyroid cell hyperfunction. No inflammatory changes were found**,** these changes may serve as ultrastructural marker for subsequent hypofunction of the gland in amiodarone-induced thyrotoxicosis.[24]

Moreover, among 83 consecutive patients operated on for thyrotoxicosis in the USA, four had a pattern of pathologic findings that were similar and unexpected; namely, involutional changes, degenerative and destructive follicular lesions, and zones of fibrosis. These four patients were being treated with amiodarone for cardiac tachyarrhythmias. Characteristically, a small percentage of involuted follicles were revealed varying degrees of damage ranging from few degenerative changes in lining cells to total follicular destruction. Damaged follicular cells were swollen with granular or vacuolated cytoplasm. This type of cytoplasmic alteration has also been reported to arise in pneumocytes and hepatocytes affected by amiodarone. So it is suggested that the drug is implicated in occurrence of the described thyroid changes (with consequent release of iodothyronines into the circulation) which is perhaps an important contributor to the associated thyrotoxicosis.[25] See figure.1

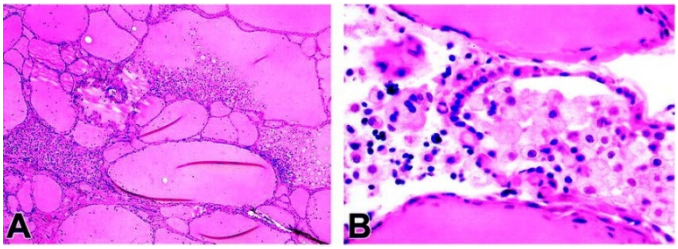


Figure 1. Type 2 amiodarone-induced thyrotoxicosis, showing scattered thyroid follicles with partial collapse and absence or reduced colloid, containing mixture of desquamated epithelial cells, foamy macrophages, and lymphocytes (hematoxylin-eosin, original magnifications ×40 [A] and ×400 [B]).[26]

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