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Thyroid Dysfunction Induced by Amiodarone Therapy

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Overview

Practice Essentials

Amiodarone is a potent antiarrhythmic drug that is used to treat ventricular and supraventricular tachyarrhythmias. It is a benzofuran-derived, iodine-rich compound with some structural similarity to thyroxine (T4). Amiodarone contains approximately 37% iodine by weight. Each 200-mg tablet is estimated to contain about 75 mg of organic iodide, 8-17% of which is released as free iodide. Standard maintenance therapy with 200-mg amiodarone can provide more than 100 times the daily iodine requirement. It is highly lipid-soluble and is concentrated in the adipose tissue, muscle, liver, lung, and thyroid gland.[1]

The elimination half-life of amiodarone is highly variable, ranging from 50-100 days; total body iodine stores remain increased for up to 9 months after discontinuation of the drug. Thyroid abnormalities have been noted in up to 14-18% of patients receiving long-term amiodarone therapy. However, a meta-analysis suggested that with the lower doses of amiodarone (150-330 mg) incidence of thyroid dysfunction is 3.7%. The effects range from abnormal thyroid function test findings to overt thyroid dysfunction, which may be either amiodarone-induced thyrotoxicosis (AIT) or amiodarone-induced hypothyroidism (AIH).[2, 3, 4, 5] Both can develop in apparently normal thyroid glands or in glands with preexisting abnormalities.

Signs and symptoms of thyrotoxicosis and hypothyroidism induced by amiodarone

Signs and symptoms of AIT include the following:

- Unexplained weight loss
- Heat intolerance or increased perspiration
- Profound muscle weakness
- Unexplained fatigue
- Emotional lability
- Frequent stools
- Oligomenorrhea
- Anxiety, nervousness, or palpitations

Signs and symptoms of AIH include the following:

- Fatigue
- Lethargy
- Cold intolerance
- Mental sluggishness
- Weakness
- Constipation
- Menorrhagia
- Dry skin

Workup in thyrotoxicosis and hypothyroidism induced by amiodarone

Lab findings for AIH are similar to those for spontaneous hypothyroidism and include decreased levels of serum free T4 and increased levels of serum thyroid-stimulating hormone (TSH). Serum thyroglobulin levels are often increased, probably because of TSH-enhanced thyroid stimulation.

Lab findings for AIT include elevated levels of serum total and serum free T4 and T3, and undetectable levels of TSH. Low TSH levels and elevated free T4 levels are also commonly seen in the early phases of amiodarone therapy and in patients with severe nonthyroidal illness who have euthyroidism and are treated with amiodarone. Therefore, the measurement of free T3 levels may be helpful in differentiating conditions, because free T3 levels are increased in hyperthyroidism, while they are decreased in early phases of treatment with amiodarone.

Although lab studies can confirm a diagnosis of thyrotoxicosis, further studies are necessary to recognize the correct type of AIT. [6] An ultrasonogram of the thyroid that shows abnormalities such as hypoechoic or nodular patterns or increased gland size is more indicative of type 1.

Management of thyrotoxicosis and hypothyroidism induced by amiodarone

The initial management of AIT involves deciding whether to discontinue amiodarone therapy. This depends on the patient's cardiac condition, the availability of alternate therapies, and the type of AIT present in the patient.

Mild AIT subsides spontaneously in up to 20% of cases upon discontinuation of amiodarone therapy.

Type 1 thyrotoxicosis is treated with high doses of thionamides (eg, methimazole [40-60 mg/d] or propylthiouracil [600-800 mg/d]) to block thyroid hormone synthesis. Adding potassium perchlorate may block iodide uptake by the thyroid and deplete intrathyroidal iodine stores. Because potassium perchlorate is a drug that potentially causes aplastic anemia, limit it to patients whose condition cannot be controlled by methimazole alone.

Type 2 thyrotoxicosis is treated with a relatively long course of glucocorticoids.

If thyrotoxicosis is exacerbated after initial control, it is usually treated with steroids. In type 1 AIT, this exacerbation may be due to mixed forms, which respond to the addition of steroids. In type 2 AIT, relapse can occur after discontinuation of corticosteroid treatment, and steroid treatment may need to be restarted.

Hypothyroidism in patients with no preexisting thyroid disease often resolves after discontinuation of amiodarone therapy. However, hypothyroidism may persist after discontinuation of treatment in patients with underlying chronic autoimmune thyroiditis and high titers of anti-thyroid peroxidase (anti-TPO) antibodies. In this case, the patient may require permanent T4 replacement therapy.

Total or near-total thyroidectomy is performed in cases of AIT that fail to respond to combination therapy with thionamides, perchlorate, and corticosteroids. Thyroidectomy is also performed in patients who need amiodarone therapy but whose resulting hyperthyroidism does not respond to medical treatment. In addition, it is carried out for immediate control of a thyrotoxic state (eg, during thyroid storm), as well as in patients with intractable arrhythmias.

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Pathophysiology

Amiodarone causes a wide spectrum of effects on the thyroid.

- Amiodarone inhibits type 1 5'-deiodinase enzyme activity, thereby decreasing the peripheral conversion of T4 to triiodothyronine (T3) and reducing the clearance of both T4 and reverse T3 (rT3). Consequently, the serum levels of T4 and rT3 increase and the serum levels of T3 decrease by 20-25%.
- Amiodarone inhibits entry of T4 and T3 into the peripheral tissue. Serum T4 levels increase by an average of 40% above pretreatment levels after 1-4 months of treatment with amiodarone. This, in itself, does not constitute evidence of hyperthyroidism (thyrotoxicosis).
- Inhibition of type 2 5'-deiodinase enzyme activity in the pituitary due to feedback regulation is seen in the first 1-3 months and leads to an increase in thyroid-stimulating hormone (TSH) levels. This is not an indication for T4 replacement in these patients. Serum TSH levels return to normal in 2-3 months as T4 concentrations rise sufficiently to overcome the partial block in T3 production. The response of TSH to thyroid-releasing hormone (TRH) may be reduced.
- Amiodarone and its metabolites may have a direct cytotoxic effect on the thyroid follicular cells, which causes a destructive thyroiditis.
- Amiodarone and its metabolite desethylamiodarone can act as a competitive antagonist of T3 at the cardiac cellular level.

In summary, serum T4 levels rise by 20-40% during the first month of therapy and then gradually fall toward high normal. Serum T3 levels decrease by up to 30% within the first few weeks of therapy and remain slightly decreased or low normal. Serum rT3 levels increase by 20% soon afterward and remain increased. Serum thyrotropin (TSH) levels usually rise after the start of therapy but return to normal in 2-3 months.

Two forms of AIT have been described. Type 1 usually affects patients with latent or preexisting thyroid disorders and is more common in areas of low iodine intake. Type 1 is caused by iodine-induced excess thyroid hormone synthesis and release (Jod-Basedow phenomenon). Type 2 occurs in patients 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 follicular cells. However, mixed forms of AIT may occur in an abnormal thyroid gland, with features of destructive processes and iodine excess.

The most likely mechanisms of AIH are an enhanced susceptibility to the inhibitory effect of iodine on thyroid hormone synthesis and the inability of the thyroid gland to escape from the Wolff-Chaikoff effect after an iodine load in patients with preexisting Hashimoto thyroiditis. In addition, iodine-induced damage to the thyroid follicles may accelerate the natural trend of Hashimoto thyroiditis toward hypothyroidism. Patients without underlying thyroid abnormalities are postulated to have subtle defects in iodine organification that lead to decreased thyroid hormone synthesis, peripheral down regulation of thyroid hormone receptors, and subsequent hypothyroidism.

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Frequency

United States

The prevalence of AIT in the United States is 3%; the prevalence of AIH is 22%. The relative prevalence of the 2 forms of AIT is unknown.

International

Some studies indicate that the incidence varies with the dietary iodine intake in the population. AIT occurs more frequently in geographical areas with low iodine intake, whereas AIH is more frequent in iodine-replete areas. However, in a Dutch study of persons with euthyroidism living in an area with moderately sufficient iodine intake, the incidence of AIT was twice that of AIH.

Mortality/Morbidity

Although amiodarone-associated thyroid dysfunction is usually a mild clinical condition, it can be severe, life threatening, and even lethal. Fatal cases of thyroid storm and myxedema coma have been reported despite various aggressive therapies.

Race

No well-described racial differences exist.

Sex

AIH is more frequent in females, with a female-to-male ratio of 1.5:1. AIT, however, is more frequent in males, with a male-to-female ratio of 3:1.

Age

The risk of AIH is higher in elderly persons,[7] probably because of the higher prevalence of underlying thyroid abnormality.

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Prognosis

The prognosis for AIT may be very poor even though a wide range of antithyroid therapy is available. This prognosis emphasizes the need for careful monitoring of patients receiving amiodarone treatment.

The long-term prognosis for AIH is usually good.

A randomized, double-blind study by Diederichsen et al indicated that in patients without previous thyroid dysfunction, short-term amiodarone use can be safe. The study looked at the effects of 8 weeks of either amiodarone or placebo therapy in 212 patients with atrial fibrillation undergoing catheter ablation. Although the amiodarone patients had higher levels of TSH, T4, and free T4, as well as lower levels of T3 and free T3, than did the placebo group, thyroid dysfunction peaked at 1 month, was declining at 3 months, and returned to baseline levels by 6 months.[8]

A study by Wang et al indicated that in patients with paroxysmal atrial fibrillation and AIT, early catheter ablation is safe and effective, although the rate of atrial tachyarrhythmia recurrence is higher than in controls for as long as 3 months after pulmonary vein isolation.[9]

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Patient Education

Instruct patients about the adverse effects of amiodarone therapy. Give them a list of potential symptom manifestations. Because the development of thyrotoxicosis is sudden and explosive, instruct patients to watch for symptoms and to seek treatment promptly.

Patients should also be aware of the potential side effects of antithyroid medications. Instruct patients to watch for signs such as fever, sore throat, jaundice, or oral ulcers.

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Presentation

History

The clinical presentation of AIH is usually subtle, while that of AIT can be dramatic, with life-threatening cardiac manifestations without antecedent subclinical biochemical findings. Suspect AIT in a patient who was previously stable while receiving amiodarone but who starts to show signs of cardiac decompensation, tachyarrhythmias, or angina. However, patients may lack cardiac manifestations because of amiodarone's intrinsic effect on the heart, and other signs of hyperthyroidism such as weight loss and fatigue may predominate. Thyrotoxicosis can occur while a patient receives amiodarone and even several months after discontinuation of treatment. Hypothyroidism is rare after the first 18 months of therapy.

- Symptoms of AIT include the following:
    - Unexplained weight loss
    - Heat intolerance or increased perspiration
    - Profound muscle weakness
    - Unexplained fatigue
    - Emotional lability
    - Frequent stools
    - Oligomenorrhea
    - Anxiety, nervousness, or palpitations
- Symptoms of AIH include the following:
    - Fatigue
    - Lethargy
    - Cold intolerance
    - Mental sluggishness
    - Weakness
    - Constipation
    - Menorrhagia
    - Dry skin
- A family history of certain conditions can also be important. Consider the following:

- Autoimmune disease
- Thyroid disease
- Medication history
- Emigration from iodine-deficient areas

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Physical

The physical signs of thyrotoxicosis or hypothyroidism induced by amiodarone therapy do not differ from those observed in states of thyroid excess or deficiency attributable to other causes.

- Signs of AIT include tremor, goiter, heart failure, sinus tachycardia, and atrial fibrillation.
- The presence of proptosis or multinodular or diffuse goiter usually indicates type 1 AIT. A small, often tender, goiter occasionally develops in patients with type 2 AIT.
- The clinical manifestations of AIH are similar to those of spontaneous hypothyroidism. Patients present with vague symptoms and signs such as fatigue, lethargy, cold intolerance, mental sluggishness, and dry skin. A goiter is found in 20% of patients with hypothyroidism who live in iodine-replete areas, but most of these goiters predate the start of amiodarone treatment. Myxedema coma has also been reported in a patient receiving long-term amiodarone therapy. In patients already receiving levothyroxine replacement therapy, the dose of levothyroxine may need to be increased to offset the amiodarone-induced inhibition of the T4-to-T3 conversion.

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Causes

The risk of developing hypothyroidism or thyrotoxicosis is independent of the daily or cumulative dose of amiodarone. However, some small studies show the contrary. Autoimmune thyroid disease is the principal risk factor for the development of hypothyroidism. High dietary intake and a positive family history of thyroid disease may also be predisposing factors. Females with thyroid peroxidase or thyroglobulin antibodies have a relative risk of 13.5% for the development of hypothyroidism.

A Japanese study, by Kinoshita et al, indicated that in patients receiving amiodarone, the presence of dilated cardiomyopathy and cardiac sarcoidosis are risk factors for amiodarone-induced hyperthyroidism, while higher baseline TSH levels and lower baseline free thyroxine levels are predictors for amiodarone-induced hypothyroidism. The investigators also stated that because the TSH and free thyroxine levels are apparent risk factors, subclinical hypothyroidism may be a predictor for amiodarone-induced hypothyroidism.[10]

A literature review by Zhong et al indicated that new-onset AIH is particularly likely to occur in older women and in regions with a high environmental iodine content. The incidence of AIH in women was reported to be 19.2%, compared with 13.3% in men, with mean age found to correlate positively with the percentage of women. In areas with a high iodine content, the incidence of AIH was 20.3%, compared with 8.7% in regions with a low iodine content.[11]

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Differential Diagnoses

- Euthyroid Sick Syndrome
- Subacute Thyroiditis

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Workup

Workup

Laboratory Studies

Lab findings for AIH are similar to those for spontaneous hypothyroidism and include decreased levels of serum free T4 and increased levels of serum TSH. Serum thyroglobulin levels are often increased, probably because of TSH-enhanced thyroid stimulation.

Lab findings for AIT are elevated levels of serum total and serum free T4 and T3, and undetectable levels of TSH. Low TSH levels and elevated free T4 levels are also commonly seen in the early phases of amiodarone therapy and in patients with severe nonthyroidal illness who have euthyroidism and are treated with amiodarone. Therefore, the measurement of free T3 levels may be helpful in differentiating conditions, because free T3 levels are increased in hyperthyroidism, while they are decreased in early phases of treatment with amiodarone. Serum rT3 levels are also markedly increased. However, serum rT3 levels are not part of a routine workup.

Because amiodarone has no effect on the serum concentration of thyroid hormone-binding globulin, changes in the levels of free T4 and free T3 mirror those for total T4 and total T3.

In the absence of hypothyroid symptoms, moderately elevated serum TSH levels with high normal or raised serum free T4 levels may reflect subclinical hypothyroidism. Close monitoring and repeat testing after 6 weeks is recommended.

Serum sex hormone–binding globulin concentration is increased in patients with AIT but not in patients with hyperthyroxinemia and euthyroidism who are treated with amiodarone therapy. This assay is of limited importance, however, because of the numerous factors that affect the serum levels.

Serum thyroglobulin levels are not diagnostic because they are usually higher in type 2 AIT but can be elevated in both types of AIT. Thyroglobulin levels can be increased in patients with goiters independent of the association with destructive thyroiditis.

In some studies, serum interleukin 6 levels were lower in type 1 AIT and markedly elevated in type 2 AIT. The fact that interleukin 6 is also increased in patients with severe nonthyroidal illnesses limits the specificity of interleukin 6 determination.

Thyroid autoantibodies are generally absent in type 2 AIT. The presence of autoantibodies supports the diagnosis of type 1 AIT. However, a test negative for autoantibodies does not rule out type 1 AIT.

Urinary iodine excretion is not helpful in the initial assessment but may be useful long after the withdrawal of amiodarone to assess whether excess iodine levels are present.

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Imaging Studies

Although the above lab studies can confirm a diagnosis of thyrotoxicosis, further studies are necessary to recognize the correct type of AIT.[6] This distinction is important when choosing treatment modalities.

- An ultrasonogram of the thyroid that shows abnormalities such as hypoechoic or nodular patterns or increased gland size is more indicative of type 1.
- Radioactive iodine uptake studies are not helpful in the United States. Normal or elevated values found in radioactive iodine uptake studies suggest type 1 AIT, but this is rarely seen in the United States. The high levels of iodine result in serum levels that compete with the tracer used to perform the uptake test; thus, test results of type 1 and type 2 usually have uptakes of less than 1%. Detectable 24-hour radioactive iodine uptake is seen in tests of most patients with AIH. This may be caused by excess stimulation of the thyroid by TSH.

Color flow Doppler ultrasonography visualizes the amount of blood flow within the thyroid. However, the accuracy of this tool is limited by the proficiency of the sonographer.

- Pattern 0 (absent vascularity, gland destruction) is associated with type 2 AIT.
- Patterns 1-3 (with vascularity) are associated with type 1 AIT.

Most patients with AIH have been reported to have positive results on the perchlorate discharge test, indicating defects in intrathyroidal iodide organification. People with AIT have negative test results. These tests are rarely indicated or performed outside an academic setting.

A study found technetium-99m – sestamibi (99m Tc-MIBI) thyroid scintigraphy to be effective in the differential diagnosis of AIT.[6, 12] According to the report, which utilized patients with either type 1 or type 2 AIT, or with an indefinite form of the condition, this modality proved superior to a variety of diagnostic tools, including color flow Doppler ultrasonography and radioactive iodine, in differentiating one form of AIT from another.

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Histologic Findings

A biopsy of the thyroid gland is unnecessary in most patients. The histological changes that occur with amiodarone administration have been studied in a research setting and include the following:

- Marked follicular disruption by diffuse fibrosis
- Epithelial atrophy
- Apoptosis
- Necrosis
- Markedly dilated endoplasmic reticulum
- Intraluminal aggregates of vacuolated cells
- Foci of nonspecific lymphocyte infiltration

Patients with euthyroidism treated with amiodarone therapy showed minimal or no evidence of thyroid follicular damage.

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Treatment

Medical Care

AIT presents a therapeutic challenge because data on optimal treatment are limited because of the lack of randomized, controlled trials.

- Differentiation of the 2 types of thyrotoxicosis is essential for determining the best management of the disease. However, one study in the United Kingdom found that the distinction between the 2 subtypes of AIT was not essential for treatment and found no difference in overall outcome between the 2 groups treated with thionamides alone. These results conflict with those of an Italian study, which found that type 2 AIT responds to steroids. This difference in results was attributed to the disparate levels of dietary iodine intake endemic to the 2 regions. The heterogeneity of patients with AIT (especially regarding iodine intake), the small number of patients studied in these trials, and the incomplete knowledge of the complex pathogenesis of the disease probably account for the contradictory results.
- The initial management of AIT involves deciding whether to discontinue amiodarone therapy. This depends on the patient's cardiac condition, the availability of alternate therapies, and the type of AIT present in the patient. Continuation of amiodarone treatment does not alter the basic approach to the medical management of thyrotoxicosis, but it reduces the chances of a successful outcome. In type 1 thyrotoxicosis, the persistently raised levels of intrathyroidal and circulating iodide reduce the effectiveness of treatment with antithyroid drugs.
- Mild AIT subsides spontaneously in up to 20% of cases upon discontinuation of amiodarone therapy. Many patients with type 2 AIT become euthyroid within 3-5 months after the discontinuation of amiodarone therapy. Occasionally, spontaneous remission occurs despite continued amiodarone use. Recurrences of type 2 AIT despite discontinuation of amiodarone have also been documented. Spontaneous remissions of type 1 AIT have not been documented.
    - Even if amiodarone therapy is stopped, thyrotoxicosis persists for up to 8 months because of the drug's long half-life. Discontinuation of the drug has no immediate benefit.
    - No randomized, controlled trials exist that determine the effect of stopping amiodarone therapy in patients with AIT. This decision is made in consultation with the cardiologist. Amiodarone therapy is usually continued unless it is ineffective in treating the arrhythmia or toxicity in other organs is evident. Moreover, stopping amiodarone therapy may exacerbate symptoms of thyrotoxicosis, as it blocks T4-to-T3 conversion and beta-adrenergic receptors. On the other hand, severe thyrotoxicosis may be incompatible with continuation of amiodarone treatment unless a thyroidectomy is performed.
- Type 1 thyrotoxicosis

- Type 1 thyrotoxicosis is treated with high doses of thionamides (eg, methimazole [40-60 mg/d] or propylthiouracil [600-800 mg/d]) to block thyroid hormone synthesis. Thionamides block hormone synthesis by blocking iodine organification and the coupling of iodotyrosines. Because of the large number of preformed thyroid hormones, the blocking effect is delayed and may take as long as 2-4 months.

- Adding potassium perchlorate may block iodide uptake by the thyroid and deplete intrathyroidal iodine stores. Thus, perchlorate prevents further synthesis of thyroid hormones and improves the therapeutic efficacy of thionamides. Some studies have found good results with adding potassium perchlorate, and some have not. Potassium perchlorate has not been approved by the US Food and Drug Administration (FDA) for the treatment of thyrotoxicosis.

- Because potassium perchlorate is a drug that potentially causes aplastic anemia, limit it to patients whose condition cannot be controlled by methimazole alone. The dose of perchlorate is 600-1000 mg/d. Do not administer potassium perchlorate for longer than 30 days because of serious adverse effects such as aplastic anemia, nephrotic syndrome, and agranulocytosis. Perform careful hematological examinations regularly during administration of potassium perchlorate.[6, 13]

- Because all antithyroid drugs can cause bone marrow suppression, instruct patients to watch for signs such as fever, sore throat, or oral ulcers. The administration of thionamides is usually tapered to a low maintenance dose and is continued until amiodarone therapy is started. If amiodarone therapy is subsequently discontinued, the thionamides are continued until urine iodine levels return to normal (usually in 6-18 mo).

- Type 2 thyrotoxicosis

  - Type 2 thyrotoxicosis is treated with a relatively long course of glucocorticoids. In addition to their membrane-stabilizing and anti-inflammatory effects, glucocorticoids reduce conversion of T4 to T3 by inhibiting type 1 5'-deiodinase activity. If the patient does not have any symptoms of thyrotoxicosis or a life-threatening arrhythmia that requires amiodarone therapy, the initial treatment would be discontinuation of amiodarone and continued monitoring of thyroid function.[6]

  - Administer prednisone at 30-40 mg/d and taper over a couple of months until free T4 levels are within the reference range. The symptoms may biochemically and clinically improve within 1 week following the start of therapy. Consider osteoporosis prophylaxis in patients at high risk for osteoporosis or in whom steroids are continued for more than 3 months.

- When the mechanism of hyperthyroidism is uncertain, a combination of glucocorticoids and thionamides is used as initial therapy. A rapid response suggests type 2 AIT; thionamides can be tapered. A poor initial response suggests type 1 AIT; the steroids can be tapered and the patient can be treated for type 1 AIT.

- Regardless of the chosen medical regimen, the toxic state invariably takes several weeks to control because of the large stores of preformed intrathyroidal hormones.

- If thyrotoxicosis is exacerbated after initial control, it is usually treated with steroids. In type 1 AIT, this exacerbation may be due to mixed forms, which respond to the addition of steroids. In type 2 AIT, relapse can occur after discontinuation of corticosteroid treatment, and steroid treatment may need to be restarted.

- If amiodarone therapy is discontinued, beta-blockers and iopanoic acid may be added to ameliorate hyperthyroid symptoms exacerbated by amiodarone withdrawal.

- Radioactive iodine can be used in the rare patients with high radioactive iodine uptake; otherwise, the iodine of amiodarone inhibits uptake by the gland. Moreover, radioactive iodine often initially exacerbates the hyperthyroid state by releasing preformed hormone that is stored in the thyroid.

- Plasmapheresis is an expensive treatment that has transient benefits and is usually followed by an exacerbation of AIT. The efficacy of lithium and iopanoic acid for the management of AIT has not been confirmed in large, randomized, controlled trials.

- Thyroid ablation is a valid management option for type 1 AIT once euthyroidism has been restored, especially if amiodarone therapy must be restarted. Type 2 AIT requires strict follow-up because of possible progression to hypothyroidism, either spontaneously or after iodine re-exposure.

Hypothyroidism in patients with no preexisting thyroid disease often resolves after discontinuation of amiodarone therapy. However, hypothyroidism may persist after discontinuation of treatment in patients with underlying chronic autoimmune thyroiditis and high titers of anti-TPO antibodies. In this case, the patient may require permanent T4 replacement therapy. Amiodarone therapy is usually continued while T4 is used to normalize the TSH level. In view of the often-severe underlying cardiac disease, consider maintaining the serum TSH concentration in the upper half of the reference range. Levothyroxine is the drug of choice because it is not associated with the spikes in serum thyroid hormone concentrations observed in patients

given L-T3, which also requires multiple daily doses. However, if amiodarone therapy is continued, larger doses of T4 are required to offset the inhibitory effects of amiodarone on the conversion of T4 to T3.

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Surgical Care

Total or near-total thyroidectomy is performed in cases of AIT that fail to respond to combination therapy with thionamides, perchlorate, and corticosteroids. Thyroidectomy is also performed in patients who need amiodarone therapy but whose resulting hyperthyroidism does not respond to medical treatment. In addition, it is carried out for immediate control of a thyrotoxic state (eg, during thyroid storm), as well as in patients with intractable arrhythmias. Treat the resulting hypothyroidism with thyroid hormone replacement. Despite the minimally elevated risk due to underlying heart disease, surgery is reasonably safe in these patients and can even be performed with local anesthesia.

A retrospective cohort study by Cappellani et al indicated that in patients with AIT and a left ventricular ejection fraction (LVEF) of less than 40%, those who undergo total thyroidectomy after euthyroidism has been restored, and thus have longer exposure to thyrotoxicosis, have a higher mortality rate (peritreatment mortality rate: 40%; 5-year cardiovascular mortality rate: 53.3%) than do those who undergo the surgery while still thyrotoxic (0% and 12.3% mortality rates, respectively). In contrast, survival rates in study patients with an LVEF of 40% or above did not significantly differ with regard to whether or not they were euthyroid when total thyroidectomy was performed.[14]

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Consultations

Consultation with an endocrinologist is recommended. Consult with a cardiologist to decide whether or not to continue amiodarone therapy.

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Diet

No dietary restrictions apply, but excess amounts of iodide found in some expectorants, contrast dyes, seaweed tablets, and health food supplements should be avoided.

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Activity

Restriction of activity is prudent in elderly persons or in patients with severe thyrotoxicosis with cardiovascular symptoms. Otherwise, no activity restrictions are necessary.

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Complications

Complications include the following:

- Hyperthyroidism, thyroid storm
- Hypothyroidism, myxedema coma
- Aplastic anemia secondary to perchlorate use
- Agranulocytosis or hepatitis secondary to thionamides

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Prevention

Test baseline thyroid function in all patients starting amiodarone therapy to exclude underlying gland dysfunction that may predispose them to thyroid abnormalities after therapy begins. The serum levels of TSH, free T4, and free T3 may be reassessed after 3 months of amiodarone therapy. In patients with euthyroidism, thyroid function results may be used as reference for future comparisons. Periodically monitor serum TSH levels and other thyroid indices if TSH levels are abnormal or clinical suspicion of thyroid dysfunction exists. The threshold for performing thyroid function tests should be low in patients who are taking amiodarone or who have in the past, as type 2 AIT has an abrupt onset. Continue to measure thyroid function for at least a year after amiodarone therapy is discontinued.

Research indicates that another benzofuran-derived drug, dronedarone (Multaq), may be a useful alternative treatment for arrhythmia. Although apparently not as effective an antiarrhythmic as amiodarone, dronedarone seems to be less toxic to the thyroid.[15] Dronedarone was approved by the FDA on July 2, 2009.

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Long-Term Monitoring

Prolonged monitoring of thyroid function tests is necessary in patients with AIT, even if they become euthyroid, as they may become hypothyroid. Recurrences are common in type 2 AIT.

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Guidelines

Guidelines Summary

In 2018, the European Thyroid Association published guidelines concerning amiodarone-related thyroid dysfunction management. Recommendations include the following[16] :

- Patients with amiodarone-induced thyrotoxicosis (AIT) should be considered at risk of an emergency treatment at any time due to the increased mortality and morbidity, particularly in the elderly and/or if a reduced left ventricular dysfunction is present
- Antithyroid drugs are recommended as the medical treatment of choice for most cases of AIT 1
- Oral glucocorticoids are recommended as the first-line treatment for AIT 2 with moderate to severe thyrotoxicosis; the decision to treat milder or subclinical forms should take into account the underlying cardiac conditions, with a close interaction with the specialist cardiologist
- Ablation of a hyperfunctioning thyroid gland with an elective thyroidectomy or radioiodine treatment, as in other forms of spontaneous hyperthyroidism, is recommended

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Questions & Answers

Overview

What is amiodarone-associated thyroid dysfunction?

What is the role of amiodarone in the pathophysiology of thyroid dysfunction?

What is the prevalence of amiodarone-associated thyroid dysfunction in the US?

What is the global prevalence of amiodarone-associated thyroid dysfunction?

What is the disease progression of amiodarone-associated thyroid dysfunction?

What are the racial predilections of amiodarone-associated thyroid dysfunction?

What are the sexual predilections of amiodarone-associated thyroid dysfunction?

Which age groups have the highest prevalence of amiodarone-associated thyroid dysfunction?

What is the prognosis of amiodarone-associated thyroid dysfunction?

What is included in patient education about amiodarone-associated thyroid dysfunction?

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