Amiodarone-induced thyroid disorders: a clinical review

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Summary

Although amiodarone is regarded as a highly effective anti-arrhythmic agent, its use may lead to alterations in thyroid gland function and/or thyroid hormone metabolism, partly because of its rich iodine content. Patients treated with amiodarone may manifest altered thyroid hormone profile without thyroid dysfunction, or they may present with clinically significant amiodarone-induced hypothyroidism or amiodarone-induced thyrotoxicosis. The former results from the inability of the thyroid to escape from the Wolff-Chaikoff effect. It prevails in areas with high dietary iodine intake, and it is readily managed by discontinuation of amiodarone or thyroid hormone replacement. Amiodarone-induced thyrotoxicosis occurs more frequently in areas with low iodine intake; it may arise from iodine-induced excessive thyroid hormone synthesis (type I) or destructive thyroiditis with release of preformed hormones (type II). Type I should be treated with thionamides alone or in combination with potassium perchlorate, whereas type II benefits from treatment with glucocorticoids. Surgery may be a feasible option for patients who require long-term amiodarone treatment.

Keywords: amiodarone; hyperthyroidism; hypothyroidism, thyroiditis

Amiodarone is a highly effective agent used for the treatment of various cardiac arrhythmias, ranging from paroxysmal atrial fibrillation to life-threatening ventricular tachyarrhythmias. However, the use of amiodarone is associated with several side-effects, including photosensitivity, corneal microdeposits, pulmonary toxicity, hepatotoxicity, peripheral neuropathy, hyperthyroidism and hypothyroidism.^{1–3} The purposes of this review are to summarise expected and abnormal changes in thyroid function and thyroid hormone metabolism in patients taking amiodarone, and to suggest guidelines for the diagnosis and management of amiodarone-induced thyroid dysfunction.

Amiodarone and thyroid physiology

Amiodarone is a benzofuran derivative containing two atoms of iodine per molecule (figure 1). This amounts to 37.5% of organic iodine by molecular weight, of which 10% is de-iodinated to yield free iodine. It has the potential to cause thyroid dysfunction because of this iodine-rich chemical structure. In the body, it is stored in adipose tissue, myocardium, liver, and lung and it has an elimination half-life of about 2–3 months.⁴ Hence, a normal daily maintenance dose of amiodarone (200–400 mg) generates about 6–12 mg of free iodine per day. This results in an iodine load that far exceeds the World Health Organisation'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.⁵

Amiodarone has many effects on thyroid physiology as well as the peripheral metabolism of thyroid hormones (box 1). These effects are also observed 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. Indeed, more than 50% of patients who receive long-term amiodarone therapy show abnormal results on thyroid function test, and the majority remain clinically euthyroid. Occasionally, amiodarone can also cause goitre without apparent thyroid dysfunction.

EFFECT ON THYROID HORMONE SYNTHESIS

The large amount of iodide released during the metabolism of amiodarone leads to an adaptive blockage of further thyroidal iodide uptake and thyroid hormone biosynthesis, the so-called Wolff-Chaikoff effect.⁶ Although this is apparent within the first 2 weeks of treatment, further exposure to iodine leads to normal resumption of thyroid hormone synthesis. This escape phenomenon from the Wolff-Chaikoff effect helps to safeguard the individual from developing hypothyroidism.^{3,7}

EFFECT ON THYROID HORMONE METABOLISM

At the extrathyroidal level, amiodarone has the specific ability to inhibit T4 5'-monodeiodination. The changes in serum thyroxine (T4), triiodothyronine (T3), reverse triiodothyronine (rT3), and thyroid-stimulating hormone (TSH) concentrations are similar to those produced by iodinated radiographic contrast agents, and the magnitude of these alterations is dose dependent. Amiodarone strongly inhibits type I 5'-monodeiodinase activity and thus the fractional conversion of T4 to T3.^{8–11} The decreased 5'-deiodination of T4 into T3 is observed in many tissues but is most pronounced in the thyroid and the liver, the latter being the main extrathyroidal T3 production site. This inhibitory action persists during and for several months after amiodarone treatment, explaining the decreased plasma and tissue T3 concentrations. Alterations in thyroid hormone dynamics occur, as the biological effects are mediated via T3 binding to the nuclear T3 receptors. The inhibition of type I 5'-deiodinase activity also results in the reduced clearance and a consequent rise in serum rT3

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Figure 1 Structure of thyroxine (T₄), 3,5,3'-triiodothyronine (T₃), 3,3',5'-triiodothyronine (reverse T₃), and amiodarone

Effects of amiodarone on thyroid physiology and thyroid hormone action

- inhibition of thyroidal iodide uptake and thyroid hormone synthesis (Wolff-Chaikoff effect)
- inhibition of fractional conversion of T₄ to T₃ intracellularly (inhibits both type I and type II 5'-deiodinase activity)
- inhibition of T₄ (±T₃) entry into cells
- direct T₃ antagonism at cardiac tissue level (mediated via active metabolite desethylamiodarone)

Box 1

concentrations.^{3 4 7 11} Conversely, inhibition of type II 5'-deiodinase activity would lead to reduced intrapituitary T₃ concentrations and this may in part account for the increase in serum TSH levels observed with amiodarone treatment.¹⁰

In addition, amiodarone indirectly affects thyroid hormone metabolism by inhibiting cellular thyroid hormone uptake. Results of kinetic studies suggested decreased transfer of T₄ from the plasma pool to rapidly exchangeable tissue pools, such as in the liver.^{11 12} This leads to decreased availability of the substrate T₄ intracellularly and hence reduced T₃ production. A selective decrease in hepatic T₄ transport was also demonstrated in hepatocytes and perfused rat liver, and an impaired T₃ uptake was observed in an anterior pituitary cell line.^{13 14}

EFFECT ON CARDIAC TISSUE

Amiodarone is a highly versatile and effective anti-arrhythmic agent. Its mechanism of action on the heart is in part linked to the complex relationship of its pharmacologic actions with thyroid hormone metabolism. Electrophysiological changes in the heart induced by chronic amiodarone treatment resemble those induced by hypothyroidism, and these effects may be nullified by concomitant administration of thyroid hormone.¹⁵⁻¹⁷ The major active metabolite of amiodarone, desethylamiodarone (DEA), acts as a competitive inhibitor of T₃ binding to the α1-thyroid hormone receptor (T₃R-α1), and as a non-competitive inhibitor with respect to β1-thyroid hormone receptor (T₃R-β1).¹⁸ In animal studies, amiodarone treatment produces a significant decrease in the cardiac β-adrenergic receptor density and heart rate without altering thyroid hormone secretion and serum T₃ level.¹⁹ The finding that amiodarone treatment decreases the cardiac β-adrenergic receptor density and resting heart rate in euthyroid but not in hypothyroid rats, supports the hypothesis that the cardiac effects of amiodarone are mediated by an antagonistic action to thyroid hormones at the cellular level.²⁰ In addition, it has been hypothesised that cellular or subcellular T₃ antagonism induced by amiodarone leads to anti-arrhythmic remodelling of cardiac cells, probably through a modulation of gene expression in ion channels and other functional proteins.^{16 17 21}

However, the role of the cardiac hypothyroid state in the genesis of anti-arrhythmic activity is still a matter of considerable controversy among investigators. Amiodarone is believed to modulate some myocardial cell functions by direct inhibition of current flow through ion channels in a manner that is independent of its effect on thyroid hormone. Studies performed *in vitro* showed that amiodarone inhibits Na⁺+K⁺-ATPase activity independent of thyroid hormone, and it blocks the sodium, potassium, and calcium channels in the heart.^{22 23}

Thyroid hormone profile in patients on amiodarone treatment

The acute effects of amiodarone administration on thyroid function was studied in 24 patients with cardiac arrhythmias during the first 10 days of treatment.²⁴ In this study, TSH levels were found to increase early and significantly throughout the study, starting from the first day of therapy and reaching a value 2.7-fold higher than the basal value by the 10th day. Total T₃ decreased progressively from the second day of study; whereas reverse T₃ progressively and significantly increased and paralleled the TSH values, reaching a value of twice the basal value by the 10th day. This was followed by a progressive and significant increase in total and free T₄ concentrations starting from the fourth day of treatment. The observed later increase in T₄ levels is probably due to both direct thyroidal stimulation (by TSH) and a reduction in T₄ clearance.²⁵

After 1–4 months of amiodarone therapy, serum T₄ levels increase by an average of 40% above pretreatment levels. It is important to note that the increase in T₄ levels is an expected finding and in itself does not constitute evidence of hyperthyroidism. Likewise, TSH levels often return to normal on chronic amiodarone administration (longer than 3 months). Normalisation of serum TSH occurs as T₄ concentrations rise sufficiently to overcome the partial block in T₃ production.²⁵ Conversely, a trend to lower plasma TSH concentrations may be observed with prolonged continuation of the drug, which may suggest a partial T₃ agonist effect in some circumstances.^{11 26} The effects of amiodarone on thyroid hormone profile in euthyroid subjects are summarised in table 1.

Amiodarone-induced hypothyroidism

Amiodarone-induced hypothyroidism (AIH) is believed to result from the inability of the thyroid to escape from the Wolff-Chaikoff effect. Thyroid

Table 1 Effects of amiodarone on thyroid hormone profile in euthyroid subjects

Parameters (serum)	Duration of treatment	
	<3 months	>3 months
T4 or free T4	↑	↑ (up to 40% > baseline)
T3 or free T3	↓	↓ or low-normal
Reverse T3	↑	↑
TSH	↑ (up to 20 mU/l)	normal
TBG	normal	normal

TBG = thyroxine-binding globulins

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.^{27 28} This may arise from an underlying thyroid abnormality, such as autoimmune thyroiditis. As many as 40% of patients who develop hypothyroidism after amiodarone administration have positive thyroid antibodies, suggesting that iodide excess could unmask some pre-existent subclinical thyroid disease to produce overt thyroid failure.^{3 29 30}

The reported incidence of AIH varies widely, ranging from 6% in countries with low iodine intake to 13% in countries with a high dietary iodine intake.^{3 7 27 29} The risk of developing hypothyroidism is independent of the daily or cumulative dose of amiodarone. However, the risk is greater in the elderly and in female patients, probably as a result of a 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 microsomal or thyroglobulin antibodies, as compared with men without thyroid antibodies.³⁰ AIH may be transient or persistent, the latter is almost always associated with an underlying thyroid disorder.²⁷ 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.³⁰

CLINICAL FEATURES AND DIAGNOSIS

The clinical features of hypothyroidism are usually vague. Fatigue, lethargy, intolerance of cold, and dry skin are commonly reported; goitre is uncommon. The diagnosis is confirmed by a raised serum TSH concentration (usually > 20 mU/l) in combination with low serum levels of free T4. 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 spite of the large iodine load during amiodarone treatment, the majority of patients with AIH have inappropriately elevated thyroid radioactive iodine uptake (RAIU) results.^{27 28}

TREATMENT

AIH may be managed by either discontinuation of amiodarone therapy or thyroid hormone replacement. Discontinuation of amiodarone may not be feasible because of the underlying indication for its use, especially in the treatment of difficult ventricular tachyarrhythmias. A safer and more reliable option is to institute thyroid hormone replacement therapy, starting with 25–50 µg levothyroxine daily and increasing at intervals of 4–6 weeks until the symptoms have resolved and the target serum T4 level is achieved.^{3 7 11} The goal of treatment is to bring serum T4 levels to the upper end of its normal range, as often seen in euthyroid patients who are receiving amiodarone. It is important to realise that patients on amiodarone can have mildly elevated serum TSH levels despite adequate thyroid hormone replacement. Over-replacement will undermine the anti-arrhythmic effect of amiodarone, believed to be mediated via an intracellular state of hypothyroidism within the cardiac tissues. In general, patients should be monitored at 6 weeks and then every 3 months.

In small studies, perchlorate treatment has been shown to restore normal thyroid function rapidly in patients with AIH.^{31 32} The drug relieves iodine-induced inhibition of thyroid hormone synthesis by its ability to discharge inorganic iodine and to block further entry of iodide into the thyroid.⁴ As perchlorate toxicity can result from either prolonged use or high dosages (> 1 g daily), it is generally not recommended, as hypothyroidism can be effectively and safely treated with thyroid hormone substitution.

In the absence of hypothyroid symptoms or thyroid antibodies, patients with moderately raised serum TSH (< 20 mU/l) but high-normal or raised serum free T4 concentrations may reflect amiodarone-induced alteration in thyroid

Table 2 Pathogenesis and clinical features of amiodarone-induced hypothyroidism (AIH) and thyrotoxicosis (AIT)

	<i>AIH</i>	<i>AIT</i>
Mechanism	persistent block in intra-thyroidal iodine organification	type I: iodine-induced excessive thyroid hormone synthesis type II: destructive thyroiditis
Predisposition	high dietary iodine intake thyroid autoimmunity	low dietary iodine intake pre-existing thyroid disease, eg, nodular goitre, autonomous nodule, latent Graves' disease
Onset	early uncommon after the first 18 months of treatment	unpredictable and variable can present after withdrawal of amiodarone treatment
Diagnosis	high TSH (usually >20 mU/l) low T4 T3 unreliable (low or normal)	low TSH (often undetectable) high T4 T3 unreliable (high or normal)
Treatment	relatively simple amiodarone withdrawal or thyroxine substitution	can be difficult amiodarone withdrawal and/or medical management or thyroidectomy

function parameters or subclinical hypothyroidism. Close monitoring may be all that is necessary in these subjects. A summary of the pathogenesis and clinical features of amiodarone-induced thyroid dysfunction is presented in table 2.

Amiodarone-induced thyrotoxicosis

Amiodarone-induced thyrotoxicosis (AIT) occurs in 2–12% of patients on chronic amiodarone treatment. Some studies indicate that the incidence varies according to the dietary iodine intake in the population; AIT prevails in areas with low iodine intake (eg, central Europe) and is rather uncommon in iodine replete areas (eg, North America and UK).^{3 7 11 29} 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.³⁰ Like hypothyroidism, there is no relation between the daily or cumulative dose of amiodarone and the incidence of thyrotoxicosis.

In patients with pre-existing thyroid abnormalities, thyrotoxicosis is believed to result from iodine-induced excessive thyroid hormone synthesis (type I AIT). Its pathogenesis is related to the effects of iodine overload on abnormal thyroid glands, such as nodular goitre, autonomous nodule or latent Graves' disease. Due to alterations in the intrinsic autoregulatory mechanisms which regulate the thyroidal iodine handling, hyperthyroidism occurs in the presence of excess iodine in susceptible individuals. This is an example of the Jod-Basedow phenomenon, similar to the occurrence of hyperthyroidism in patients with endemic iodine-deficient goitre upon iodine exposure. Therefore, type I AIT could indicate the unmasking of an underlying thyroid abnormality or iodine deficiency by amiodarone treatment.^{3 7}

In patients with an apparently normal thyroid gland, thyrotoxicosis results from glandular damage with consequent release of preformed thyroid hormones into the circulation (type II AIT). Studies *in vitro* had shown amiodarone to be cytotoxic to FRTL-5 thyroid cells; this effect was inhibited by treatment with dexamethasone or perchlorate.³³ Similarly, moderate to severe follicular damage and disruption were demonstrated on histopathologic study of thyroid glands obtained from patients with type II AIT.^{33 34} The finding of markedly elevated serum levels of interleukin-6 (IL-6) in type II AIT patients further supports this destructive-cum-inflammatory process, whereas normal or slightly elevated levels of IL-6 are found in type I AIT patients.^{35 36}

Thyrotoxicosis in type II AIT patients is usually self-limiting, which may be explained by the dose-dependent cytotoxic effect of amiodarone. When intrathyroidal amiodarone concentrations exceed a certain threshold, cell damage leads to thyrotoxicosis as the contents of the thyroid leak into the bloodstream. The intrathyroidal concentration of amiodarone would also decrease, allowing repair and the restoration of euthyroidism.³⁷ Occasionally, hypothyroidism requiring levothyroxine substitution may result from extensive follicular damage.³⁸

CLINICAL FEATURES AND DIAGNOSIS

Thyrotoxicosis is suspected if patients on amiodarone treatment develop unexplained weight loss, sweating, tremor, sinus tachycardia or worsening of the underlying cardiac disorder. Similarly, AIT should be considered if there is new onset of supraventricular arrhythmias such as atrial tachycardia or atrial fibrillation. Features differentiating type I from type II AIT are summarised in table 3; however it should be recognised that both pathologic processes may co-exist in the same gland. Patients with type I AIT normally have underlying multinodu-

Table 3 Features differentiating type I from type II AIT*

	Type I	Type II
Pre-existing thyroid abnormality	present	absent
Neck examination	multinodular or diffuse goitre	normal or small tender goitre
Course of thyrotoxicosis	protracted	typically transient
Radioactive iodine uptake	normal to high	low to absent
Serum IL-6 level	normal to slightly high	extremely high
Colour flow Doppler for parenchymal blood flow	present	absent

*A distinct differentiation is not always possible as some patients may have coexistent type I and type II AIT.

lar or diffuse goitre, whereas those with type II AIT may possess a small tender goitre on examination. However, patients may not present with the classical symptoms of thyrotoxicosis which, in those with tender goitre, may occasionally be confused with subacute thyroiditis. The development of thyrotoxicosis is often unpredictable; its onset is usually sudden and explosive without antecedent subclinical biochemical findings.^{3 7 11 30} It is therefore important to educate patients to watch for features of thyrotoxicosis and to seek treatment promptly.

Thyrotoxicosis is diagnosed biochemically by a marked increase in serum levels of free T4 (or high total T4 and free thyroxine index), with serum TSH often suppressed to undetectable levels. 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 is useful to determine the most appropriate treatment. Thyroid RAIU study may be helpful in this regard, as the 24-hour uptake is usually normal-to-high in patients with type I AIT and low-to-suppressed in type II AIT.^{28 39 40} Measurement of circulating IL-6 levels also appears to be a promising discriminator but this is not widely available.^{35 36} In a recent study, colour flow Doppler sonography was found to permit rapid differentiation between the two types of AIT. In the evaluation of 27 consecutive patients by this technique before starting antithyroid treatment, parenchymal blood flow was demonstrated in all type I AIT patients while it was absent in all type II AIT patients.⁴¹

TREATMENT

Unlike hypothyroidism, which is relatively easily treated with thyroid hormone replacement, the management of hyperthyroidism can be difficult and treatment strategies must be tailored individually. 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. Conversely, patients with underlying thyroid gland abnormality may have persistent thyrotoxicosis even several months after amiodarone withdrawal.^{11 39} The discontinuation of amiodarone is feasible only if the underlying cardiac arrhythmias are not life-threatening and can be satisfactorily controlled with alternative drugs. In addition to withdrawal of amiodarone, definitive treatment of thyrotoxicosis includes the use of thionamides, high-dose corticosteroids, perchlorate, lithium, plasmapheresis, and surgery.

The medical management of patients with AIT is summarised in box 2. In patients with abnormal thyroid glands and severe thyrotoxicosis (type I AIT), thionamides can be used to block thyroid hormone synthesis. However, high doses are required (eg, carbimazole or methimazole 40–60 mg/day, or propylthiouracil 100–150 mg qid) as thionamides are less effective in the presence of high intrathyroidal iodide concentrations. Although the dose may be reduced in most instances after 6–12 weeks, long-term antithyroid medication is usually required for patients on continued amiodarone treatment.^{3 7 36 42} Some investigators prefer to continue antithyroid drugs so as to maintain complete or partial block of thyroid hormone synthesis as long as the patients are on amiodarone treatment, and to use levothyroxine substitution if hypothyroidism develops.⁴³ Occasionally, treated individuals may remain hypothyroid even after withdrawal of the antithyroid drug.⁴²

If thyrotoxicosis is severe or inadequately treated with thionamides, potassium perchlorate (250 mg 6 hourly) 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.⁴⁴ It is concentrated by the thyroid tissue in a manner similar to iodide but is not significantly metabolised in the gland or peripherally. The combination of potassium perchlorate and methimazole treatment appears to be particularly effective in patients with severe thyrotoxicosis, most probably because perchlorate inhib-

Medical management of amiodarone-induced thyrotoxicosis

Type I

Mild: thionamides alone (high dose)

- carbimazole or methimazole 40–60 mg/day
- propylthiouracil 100–150 mg qid

Moderate to severe: discontinue amiodarone (if possible); addition of perchlorate

- potassium perchlorate 250 mg qid for 4–6 weeks

or addition of lithium

- lithium carbonate 200–400 mg tid
- titrate dose to keep drug level between 0.6–1.2 mEq/l

Type II

Glucocorticoids (moderate to high dose): prednisone 0.5–1.25 mg/kg bw/day for 3–6 weeks

Box 2

its the active transport of iodide into the thyroid while methimazole blocks the intrathyroidal synthesis of thyroid hormones.^{39 43 45} The perchlorate should be tapered-off and stopped after a period of 4–6 weeks, while methimazole is continued until the restoration of euthyroidism. Long-term use of perchlorate is not advocated because of its association with fatal aplastic anaemia.⁴⁴

High-dose glucocorticoid therapy may be useful if thyrotoxicosis is not controlled or if exacerbation occurs. Steroids help by inhibiting 5'-deiodinase activity and perhaps also by affecting the thyroid gland directly. However, the adverse effects associated with high-dose steroids reduce the attractiveness of this option. Moreover, the reduction of steroid dose may be associated with recurrence of thyrotoxicosis.^{7 36 46}

In patients with apparently normal thyroid glands (type II AIT), thyrotoxicosis is usually transient and resolves upon withdrawal of amiodarone. Occasionally, spontaneous remission may occur despite continued amiodarone use.^{11 37} However, treatment with corticosteroids (eg, prednisone 40–60 mg/day) leads to faster recovery from this inflammatory or destructive form of thyroiditis. In a study of 24 consecutive patients, normal serum free T3 concentrations were achieved after a mean of 8 days in type II AIT patients on prednisone, compared with an average of 4 weeks in type I AIT patients treated with a combination of methimazole and potassium perchlorate.³⁶

More recently, the use of lithium carbonate in AIT patients with more severe thyrotoxicosis has been shown to effect more rapid normalisation of thyroid function. In this study, involving 21 AIT patients, the time course to restoration of normal thyroid function in patients treated with a combination of lithium and propylthiouracil was uniformly 4–5 weeks, compared with a mean of greater than 10 weeks in patients on propylthiouracil alone.⁴⁷ In addition to inhibiting the release of thyroid hormones, lithium is also believed to influence thyroid hormone production. As amiodarone was withdrawn from all subjects in the above study, further studies are needed to find out whether lithium therapy remains efficacious in those who need continued amiodarone treatment. To avoid the potential complications associated with lithium carbonate therapy, therapeutic drug monitoring should be performed to maintain serum lithium concentrations within the therapeutic range (0.6–1.2 mEq/l).⁴⁸

It is important to realise that the adjuvant use of β -adrenergic antagonists for symptomatic relief of thyrotoxicosis is sometimes contraindicated in patients with compromised myocardial function; furthermore, the combination with amiodarone may give rise to bradycardia and sinus arrest.¹¹ 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. This results in rapid control of thyrotoxicosis and permits continued therapy with amiodarone, although patients must be able to withstand the stress of surgery.^{49 50}

Radioactive iodine is generally not effective in treating patients with AIT, because the prevailing high iodide concentration prevents sufficient thyroidal uptake of the radioisotope.¹¹ Furthermore, this may lead to an initial exacerbation of the hyperthyroid state due to release of preformed hormones. In areas of borderline iodine deficiency, however, patients with diffuse or nodular goitres may have normal to high RAIU despite the presence of AIT.⁴⁰ It appears possible that the thyroid fails to adapt normally to the excess iodide load in these individuals; presumably these patients may respond to radioactive iodine therapy. Plasmapheresis has occasionally been tried, although not always successfully, to ameliorate severe thyrotoxicosis refractory to medical therapy.^{51 52}

Monitoring of thyroid function in amiodarone-treated patients

Baseline thyroid function tests should be performed in all patients to exclude underlying gland dysfunction that may predispose to hypo- or hyperthyroidism after amiodarone therapy is started. Serum levels of TSH, free T4, and T3 may be re-assessed after 3 months of therapy with the drug. In euthyroid subjects, thyroid function results obtained at this stage are used as reference values for future comparisons. Subsequent follow-up involves periodic monitoring of serum TSH concentrations, whereas other thyroid indices are determined only if patients showed abnormal TSH results or clinical suspicion of thyroid dysfunction. Figure 2 represents the suggested algorithm for monitoring thyroid function tests in amiodarone-treated patients.

Conclusion

Amiodarone induces alterations in thyroid hormone levels by actions on thyroidal secretion, on the peripheral tissues, and probably also on the pituitary gland.

Summary points

- amiodarone is a highly effective anti-arrhythmic agent but its use is associated with numerous side-effects
- as an iodine-rich compound, the drug has many effects on thyroid physiology as well as thyroid hormone metabolism
- the cardiac effects of amiodarone may be in part mediated by an antagonistic action to thyroid hormone by its metabolite, desethylamiodarone, at the cellular or subcellular level
- AIH prevails in populations with high dietary iodine intake; it results from the inability of the thyroid to escape from the Wolff-Chaikoff effect and is readily managed by either discontinuation of amiodarone or thyroid hormone replacement
- AIT prevails in areas with low iodine intake; it may arise from either iodine-induced excessive thyroid hormone synthesis (type I) or destructive thyroiditis with release of preformed hormones (type II)
- type I AIT usually occurs in patients with underlying thyroid abnormality and treatment commonly includes the use of thionamides and perchlorate, while surgery is reserved for refractory cases
- type II AIT commonly occurs in patients with apparently normal thyroid glands; thyrotoxicosis is often transient and resolves upon withdrawal of amiodarone, recovery is accelerated by glucocorticoid therapy
- monitoring of thyroid function should be performed in all amiodarone-treated patients to facilitate early diagnosis and treatment of amiodarone-induced thyroid dysfunction

Box 3

Figure 2 Algorithm for monitoring of thyroid function tests in amiodarone-treated patients

These actions result in elevations in serum T4 and rT3 concentrations, transient increases in TSH concentrations, and decreases in T3 concentrations. Both hypothyroidism and hyperthyroidism are prone to occur in patients receiving amiodarone. A proper understanding of the effects of amiodarone on thyroid physiology and thyroid hormone metabolism is thus crucial for the interpretation of thyroid function results in amiodarone-treated individuals. To complicate matters further, the results of standard thyroid function tests are often compounded by non-thyroidal illnesses. Therefore, it remains a challenging task for clinicians to ensure the appropriate diagnosis, monitoring and treatment of patients with amiodarone-induced thyroid dysfunction.

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