FOR DEBATE — DIAGNOSIS AND MANAGEMENT PROTOCOLS

DIAGNOSIS AND MANAGEMENT OF AMIODARONE-INDUCED HYPERTHYROIDISM

Amiodarone (Cordarone-X) is an effective iodine-rich anti-arrhythmic agent for the prophylaxis and treatment of many cardiac rhythm disturbances. Unlike many other anti-arrhythmic drugs amiodarone appears to be safe in patients with significant left ventricular dysfunction, and may offer prognostic benefit for some patients. It has a remarkable structural resemblance to thyroid hormones and contains 39% iodine by weight. It is only metabolised and excreted very slowly and its biological half-life may be as long as 4 months.

Amiodarone may cause both hyper- and hypothyroidism. Hypothyroidism is easily controlled by amiodarone withdrawal and a short course of potassium perchlorate if the condition is transient, or by L-thyroxine replacement in permanent forms.

In contrast, amiodarone-induced hyperthyroidism is a more complex therapeutic challenge. Proposed treatment regimens have not been uniformly successful, probably because of incomplete knowledge of the pathogenesis of this condition. Its diagnosis and treatment is often rather difficult and the opinion of an endocrinologist is recommended in all cases.

Amiodarone hyperthyroidism occurs more frequently in men and in iodine-deficient areas, with a reported incidence of 2 - 13%. There seems to be no relation between this condition and the daily or the cumulative dose of amiodarone. Onset of the hyperthyroidism is often acute and may occur even several months after treatment has been discontinued.

DIAGNOSIS

Although diagnosis of the hyperthyroidism may be straightforward, its clinical features can be obscured by the anti-adrenergic effects of amiodarone. New or recurrent atrial arrhythmias during long-term treatment should arouse suspicion of amiodarone-induced hyperthyroidism.

In clinically euthyroid patients on long-term amiodarone treatment (more than 3 months), the free T_4 level is usually normal or slightly raised with low-normal free T_3 and TSH values. When these patients become hyperthyroid the biochemical diagnosis is usually easy with the free T_3 being raised together with TSH values suppressed to undetectable concentrations.

Two main forms of amiodarone-induced hyperthyroidism with differing aetiologies and requiring different treatment have been identified (Table I). Type I occurs in an abnormal thyroid (nodular goitre or latent Graves' disease), while type II develops in an apparently normal thyroid. The former is due to iodine-induced increased thyroid hormone synthesis (Jod-Basedow phenomenon) and the latter to iodine- or amiodarone-induced thyroid damage (chemical subacute destructive thyroiditis) with consequent leakage of preformed thyroid hormones into the circulation. It is important to distinguish between type I and II hyperthyroidism as it has a major influence on subsequent management.

Table I. Diagnosis of amiodarone-induced hyperthyroidism

	Type 1	Type II
Underlying thyroid abnormality	Yes	No
Pathological mechanism	Increased hormone production (Jod-Basedow effect)	Chemical thyroiditis
Goitre	Multinodular or diffuse	Small, may be tender
Radioactive I/Tc uptake	Normal/increased	Low/absent
Interleukin-6	Normal/moderately raised	Markedly raised
Thyroid ultrasound	Nodular/enlarged	Normal

Clinical evidence of a multinodular goitre or Graves' ophthalmopathy is usually only found in type I hyperthyroidism. A small, often tender, goitre may be found in type II hyperthyroidism. The most useful investigation to distinguish between these two conditions is an uptake test with either technetium-99m or radioiodine (I-131 or I-123). Uptake is normal or raised in type I hyperthyroidism, but is very low or absent in type II disease due to damage to or destruction of the thyroid. Other tests that may be useful are interleukin-6 determinations and thyroid ultrasonography.

The diagnosis of type I or II hyperthyroidism is not always clear cut. Some patients show a mixed picture, combining evidence of a superimposed thyroiditis with that of pre-existing thyroid disease.

MANAGEMENT

If amiodarone was prescribed for a non-life-threatening arrhythmia, replacing it with an alternative form of treatment should be considered. However, due to their β-adrenergic blocking activity amiodarone and its metabolites may protect the patient from some of the effects of the hyperthyroidism. Worsening of the patient's thyrotoxic symptoms and cardiac condition may indeed occur following withdrawal of amiodarone.

Type I

In type I hyperthyroidism withdrawal of amiodarone alone is rarely sufficient; most patients will remain hyperthyroid many months after stopping the medication. Management in these patients centres upon the use of carbimazole to block hormone synthesis while amiodarone and its associated iodine are cleared from the body. The effectiveness of carbimazole treatment is reduced by the markedly raised thyroidal iodine concentrations. High doses of carbimazole, 40 - 60 mg daily, are therefore required. Propylthiouracil, 100 - 150 mg 4 times a day, can also be used and has the theoretical advantage that it also inhibits peripheral 5'deiodinase activity. In addition potassium perchlorate, 0.5 g twice daily, should be considered to block iodine uptake and to improve the efficacy of carbimazole. Antithyroid medication may be continued for 3 - 6 months. Since most of these patients will have underlying Graves' disease or toxic multinodular goitre, the hyperthyroidism usually recurs after stopping the antithyroid medication. Should this happen definitive treatment, usually radioiodine, is recommended. Radioiodine treatment should only be given when adequate uptake of iodine can be demonstrated using I/Tc uptake measurements.

Subtotal or, ideally, near-total thyroidectomy may have to be considered, especially if withdrawal of amiodarone is not possible, as in intractable arrhythmias only controllable with amiodarone. Thyroidectomy may also be indicated if immediate control of the hyperthyroidism is required, as during thyroid storm or severe cardiac failure.

Plasmapheresis has been used in severely ill patients, although not very successfully, and surgery seems to offer a better outcome in these acutely ill patients.

Type II

Steroid therapy accelerates recovery with decreases in free T_3 and interleukin-6 levels within a few days. Although prednisone (40 - 60 mg daily) in all cases has been suggested by some authors, it should be kept in mind that these high levels of corticosteroids have to be given for several months. Withdrawal of amiodarone may suffice in patients with mild symptoms of hyperthyroidism and no worsening of their cardiac condition. Symptoms may be alleviated with β-adrenergic blocking agents such as propranolol. Owing to the long half-life of amiodarone, the majority of patients will only become euthyroid 3 - 5 months after withdrawal of amiodarone.

Although antithyroid medication has been suggested in this condition, it is not surprising that it has been found that steroid treatment alone is sufficient in type II hyperthyroidism, as the low radioactive uptake studies in this condition indicate a very low rate of iodide organification. Onset of type II hyperthyroidism may be explosive and the course of the disease is often difficult to predict. It may develop at any time during amiodarone treatment, often accelerating in severity over only a few days. After recovery, most type II patients remain euthyroid, but some may develop hypothyroidism spontaneously or when again exposed to an iodine load. Careful long-term follow-up of thyroid function is indicated in these patients.

Mixed forms of amiodarone-induced hyperthyroidism are usually treated with a combination of both antithyroid medication and steroids, at least initially.

Distinction of the different forms of amiodarone-induced hyperthyroidism is essential for its successful management. Type II disease should normally be treated with glucosteroids; type I should be treated with carbimazole and potassium perchlorate. Exacerbation of hyperthyroidism, which may occur in both forms and is probably related to destructive changes in the thyroid, should be controlled by the addition or increase of glucosteroids.

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Selected reading

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