Management of amiodarone-induced thyrotoxicosis

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Thyrotoxicosis occurs in up to 3% of people prescribed amiodarone in the UK. The management of amiodarone-induced thyrotoxicosis remains a clinical challenge, as data on optimal treatment from controlled trials are not available. This review will focus on current lines of management.

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Amiodarone is an iodine-rich drug which is widely used for the management of ventricular and supraventricular arrhythmias. It is a benzofuranic derivative which contains approximately 37% iodine by molecular weight and has a similar structure to thyroid hormones (Martino et al, 2001) (*Figure 1*). Amiodarone treatment is associated with alterations in thyroid physiology resulting in changes in biochemical profiles. The majority of patients remain clinically euthyroid but up to 14% of patients develop thyroid dysfunction, either hypothyroidism or hyperthyroidism, depending on dietary iodine intake (Harjai and Licata, 1997).

Amiodarone inhibits the 5'-deiodinase activity and inhibits thyroid hormone entry into peripheral tissues (Sogoll et al, 1983). These effects may result in a slight increase in free thyroxine (T_4) concentration and a decrease in serum free tri-iodothyronine (T_3) concentration in euthyroid patients given long-term amiodarone therapy. Administration of amiodarone results in an increase in serum thyroxine-stimulating hormone (TSH) during the early months of treatment but this usually normalizes later (Martino et al, 2001) (*Table 1*).

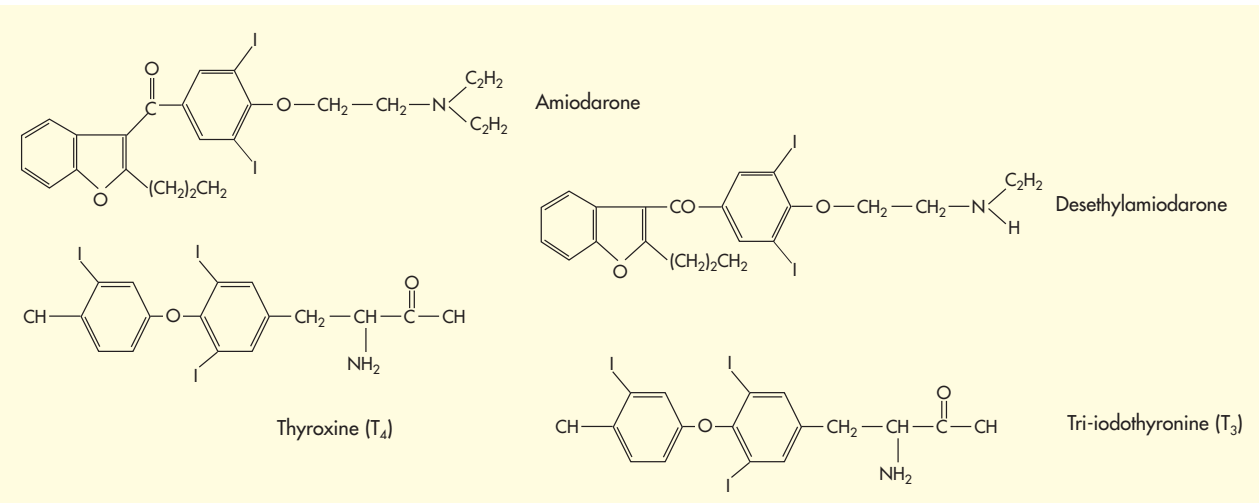

Figure 1. Molecular structure of amiodarone, desethylamiodarone, thyroxine and tri-iodothyronine.

AMIODARONE-INDUCED THYROTOXICOSIS

In the UK approximately 3% of patients treated with amiodarone develop thyrotoxicosis (Newman et al, 1998). The pathogenesis of amiodarone-induced thyrotoxicosis (AIT) is poorly understood, but it appears to be more frequent in areas with low iodine intake (Harjai and Licata, 1997). There appears to be no relationship between AIT and the daily or cumulative dose of amiodarone. Furthermore AIT may develop some months after drug withdrawal

because of the long half life of amiodarone and its metabolites (Martino et al, 1987). A relative male preponderance has been reported (Harjai and Licata, 1997).

Although not universally accepted, it has been suggested by some workers that two main forms of AIT exist, type 1 and type 2 (Bartalena et al, 1994; Newman et al, 1998). Type 1 AIT occurs in patients with an abnormal thyroid, predominantly multinodular goitre or latent Grave's disease. The iodine load associated with amiodarone triggers increased synthesis of thyroid hormones, also known as the Jod–Basedow effect. Type 2 AIT occurs as a result of a destructive 'thyroiditis' in a previous normal gland with consequence leakage of preformed thyroid hormones into the circulation. In both types of AIT a raised free T_3 and suppressed TSH to undetectable values is characteristic. *Table 2* describes the characteristics of the two subtypes of AIT.

CLINICAL PRESENTATION

Clinical examination may reveal an enlarged nodular goitre or Grave's ophthalmopathy strongly indicating type 1 AIT, whereas the gland may be impalpable in type 2 AIT. Classical symptoms of thyrotoxicosis may be absent because of the anti-adrenergic actions of amiodarone and its impairment of conversion of T_4 to T_3. AIT may be heralded as a worsening of underlying cardiac disease with tachyarrhythmias or angina (Martino et al, 1987). Imaging techniques using radioactive iodine uptake, ultrasound or colour flow Doppler may be useful in distinguishing between the subtypes (*Table 2*) (Martino et al, 1988; Eaton et al, 2002).

THERAPEUTIC OPTIONS

The management of AIT is difficult and there is no universal practice. Some workers have claimed treatment should depend on whether a patient has type 1 or 2 AIT (Martino et al, 2001), whereas others have argued against this approach and recommend management which is independent of the type of AIT (Osman et al, 2002). These conflicting findings may reflect differences in iodine intake in the various reports.

In type 1 AIT, the high intrathyroidal iodine content reduces the effectiveness of thionamide drug therapy. The goal of treatment is to block further organification of iodine and synthesis of thyroid hormones. Larger than usual daily doses of carbimazole (40–60 mg) or propylthiouracil (600–800 mg) are often necessary (Martino et al, 2001). In addition potassium perchlorate can be added to thionamides because it inhibits iodine thyroid uptake, thus contributing to depletion of intrathyroidal stores (Martino et al, 1986). Type 1 AIT often reoccurs after stopping treatment and definitive therapy such as radioactive iodine is often warranted.

In type 2 AIT, thionamides with or without potassium perchlorate are thought not to be appropriate therapy, as type 2 AIT is often a destructive thyroiditis induced by amiodarone. Corticosteroids have been successfully used and probably work via their membrane stabilizing and anti-inflammatory effects (Martino et al, 2001). Steroids have been used in daily doses of prednisolone 15–80 mg or dexamethasone 3–6 mg (Martino et al, 1986). Further definitive treatment in type 2 AIT is often not required as most patients remain euthyroid or develop hypothyroidism following discontinuation of

TABLE 1.
Effects of amiodarone on thyroid function tests in euthyroid, hypothyroid and hyperthyroid patients

Euthyroid	Free T_4 normal or slightly raised
	Free T_3 low or normal
	TSH normal or increased slightly
Hypothyroid	Free T_4 low
	Free T_3 low
	TSH raised
Thyrotoxicosis	Free T_4 raised
	Free T_3 raised
	TSH suppressed

T_4 = thyroxine; T_3 = tri-iodothyronine; TSH = thyroid-stimulating hormone.

TABLE 2.
Characteristics of the two subtypes of amiodarone-induced hyperthyroidism

Subtype	Characteristic
Type 1	Occurs in abnormal thyroid gland, nodular goitre or latent Grave's disease
	Radioactive iodine uptake normal or high
	Thyroid ultrasound reveals a large nodular gland
	Reduced blood flow on colour Doppler ultrasonography
	Managed with thionamides with or without potassium perchlorate
Type 2	Occurs in normal gland. Small, often tender thyroid
	Radioactive iodine uptake absent or low
	Thyroid ultrasound normal
	Normal or decreased colour flow Doppler ultrasonography
	Managed with corticosteroids

glucocorticoids. In patients with mixed forms with features of both types 1 and 2 AIT combination treatment with thionamides, corticosteroids and potassium perchlorate has been suggested.

Other authors have evaluated the use of thionamides in AIT regardless of the two subtypes. A recent study in 28 patients from the UK, an iodine-replete area, found satisfactory control of AIT in the vast majority of patients treated with thionamides with only one patient requiring adjuvant steroid usage (Osman et al, 2002). No differences in overall outcome between type 1 and 2 AIT were found, suggesting that thionamides may be an appropriate first-line therapy irrespective of classification.

The question as to whether amiodarone therapy should be continued or stopped when AIT occurs is difficult to answer. It may be possible to discontinue amiodarone in non-life-threatening arrhythmias but because amiodarone has a hypothyroid-like effect on the heart it may paradoxically protect the heart from the excess of thyroid hormone. Osman et al (2002) found that stopping or continuing amiodarone therapy did not influence the clinical outcome in AIT.

Other forms of treatment include radioactive iodine treatment and thyroidectomy. Use of radioiodine is possible but in most cases this is not feasible because of the low or suppressed thyroidal radioiodine uptake (Martino et al, 1988; Eaton et al, 2002). Surgical management of AIT has been claimed to be a valid alternative to medical treatment with some success, although the risks associated with thyroid storm and anaesthesia may preclude thyroidectomy (Gough and Gough, 2002).

CONCLUSIONS

There are conflicting reports on the optimal management of AIT. The use of thionamide alone as a first-line therapy has been recommended by some workers (Osman et al, 2002). Others have suggested that distinction between type 1 and 2 AIT is essential for management and recommend that type 1 should be treated with both thionamides and potassium perchlorate and type 2 be treated with glucocorticoids (Bartalena et al, 1996). Stopping or continuing amiodarone therapy does not appear to influence the clinical outcome. Further prospective studies on the various treatments of this potential life-threatening condition are required to evaluate the best strategy. **HM**

Conflict of interest: none.

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KEY POINTS

- Amiodarone-induced thyrotoxicosis (AIT) occurs in up to 3% of individuals
- AIT may be heralded as a worsening of underlying cardiac disease and classic symptoms of thyrotoxicosis may be absent.
- Type 1 AIT occurs in patients with underlying thyroid disease such as a multinodular goitre or Grave's disease.
- Type 2 AIT occurs as a result of a destructive thyroiditis with preformed thyroid hormone release.
- Thionamides, potassium perchlorate and corticosteroids are first-line treatment options for AIT.