Thyroid dysfunction in long-term amiodarone therapy

Amiodarone is a commonly prescribed medication that frequently causes thyroid dysfunction. Monitoring and treatment of this complication is therefore essential for patients taking long-term therapy.

Dr Rob Ghosh Specialist Registrar, Department of Geriatric Medicine, Robert Hadfield Wing, Northern General Hospital, Herries Road, Sheffield S5 7AU, UK.
email robinghosh@nhs.net

Amiodarone is an iodine-rich drug commonly used to treat arrhythmias. Although no longer first-line therapy for many conditions, it is still recommended for various tachyarrhythmias.[1,2] The incidence of tachyarrhythmias increases with age,[3] and coupled with the growing elderly population, we might see widespread chronic use of this drug in the future. Therefore, doctors involved in caring for older patients should be aware of amiodarone's potential side-effects (Box 1). Overall, 15% of patients taking amiodarone develop thyroid dysfunction; 13% develop hypothyroidism; and 2% have thyrotoxicosis.[4]

Current recommendations are that thyroid function be checked on initiation of treatment and then at 6-monthly intervals.[5] Thyroid hormone levels are physiologically altered by amiodarone; therefore, knowledge of the normal physiological response to amiodarone is necessary for accurate interpretation of thyroid function tests.

Box 1: Side-effects of amiodarone therapy[3]

- Hypothyroidism
- Hyperthyroidism
- Photosensitivity
- Alopecia
- Slate-grey skin discolouration
- Pulmonary fibrosis
- Asymptomatic abnormal liver funtion tests
- Hepatitis
- Peripheral neuropathy

Normal thyroid effects of amiodarone

The normal effects of amiodarone on the thyroid can be subdivided into acute (in the first 3 months of treatment) and subacute (after months; Table 1).[6] In the acute phase, decreased 5'deiodase activity contributes to an increase in serum thyroxine (T4) levels and a decrease in tri-iodothyronine (T3) levels. Because of decreased T3 feedback, thyroid-stimulating hormone (TSH) concentrations transiently increase within a few days of starting amiodarone. The level of this hormone usually falls over the next 1–3 months to baseline levels or slightly below. This is known as the Wolff-Chaikoff effect. The subacute phase is characterised by T4 levels in the high–normal reference range (around 40% above baseline), T3 levels in the lower end of normal or slightly below the reference range, and TSH levels as normal.

Amiodarone-induced hypothyroidism

In clinical hypothyroidism, TSH levels are usually >20 mU/l, and T4 levels are usually low. T3 levels are unreliable because the normal physiological response to amiodarone is for T3 to be low. Management depends on the presence of thyroid autoantibodies and whether amiodarone can be stopped.

Positive thyroid autoantibodies suggest pre-

Table 1: Physiological response to amiodarone

	Acute (<3 months)	Subacute (>3 months)
Thyroid-stimulating hormone (TSH)	Increased from baseline (<20 mU/l)	Return to baseline
Thyroxine (T4)	Moderate increase	40% increase from baseline levels, usually within reference range
Tri–iodothyronine (T3)	Decrease to lower levels of reference range or slightly below	Decrease to lower levels of reference range or slightly below

existing subclinical thyroid disease.[6] These patients are likely to require long-term thyroxine therapy. Stopping amiodarone is usually successful in restoring the euthyroid state within 2–4 months in people without autoantibodies.[7]

If stopping amiodarone is deemed inappropriate, all patients should be given long-term thyroxine to bring TSH to within normal range. A grey area exists for patients having TSH between 4·3 mU/l and 20 mU/l, and T4 within the normal range.

Raised thyroid autoantibodies suggest pre-existing thyroid disease, and the likelihood of progression to clinical hypothyroidism. Symptomatic patients require long-term thyroxine since short courses often lead to relapses.

Asymptomatic patients are likely to develop symptoms and should be monitored. Those with negative thyroid autoantibodies and symptoms often respond to a 3-month course of thyroxine.[7] This can then be stopped with follow-up thyroid function testing at 6 weeks and then 3 monthly intervals if stable.[6] Patients with no symptoms or autoantibodies can be followed up at 6-weekly then 3-monthly intervals if stable.

Amiodarone-induced thyrotoxicosis

Thyroid-stimulating hormone is low with a normal or raised T4; T3 remains at the lower end of normal. Amiodarone-induced thyrotoxicosis may occur either in the presence of underlying thyroid disease (type I) or in apparently normal thyroid glands (type II).[8]

Type 1 is due to iodine-induced excessive hormone synthesis and patients usually have underlying Grave's disease or multinodular goitre. Ultrasound shows a large hypoechoic and nodular thyroid. The radioactive iodine uptake test shows normal or increased iodine uptake (Table 2).

Type-2 amiodarone-induced thyrotoxicosis is due to amiodarone related destructive thyroiditis. Ultrasound appearance is normal in these patients, but uptake of radioactive iodine is decreased. The differentiation of type-1 or type-2 amiodarone-induced thyrotoxicosis is important as it influences treatment (Table 2).[6]

Stopping amiodarone is often undesirable and theoretically dangerous where arrhythmias may be potentiated by thyrotoxicosis. Decisions should be taken on an individual patient basis, and where amiodarone is to be stopped other antiarrhythmics should be considered.

Type-1 amiodarone-induced thyrotoxicosis

Stopping amiodarone in patients with type-1 amiodarone-induced thyrotoxicosis is rarely successful; most patients are still hyperthyroid 6–9 months after discontinuation of the drug.[7] Therefore, high doses of carbimazole are used while the amiodarone is cleared from the body.[9] Although some patients will remain euthyroid after a 3–6 month course of carbimazole, due to the underlying thyroid disease many patients will relapse and require further treatment. Definitive treatment such as with radio-iodine is often recommended.[6]

Type-2 amiodarone-induced thyrotoxicosis

Where amiodarone can be stopped, the mainstay of treatment of type-2 amiodarone-induced thyrotoxicosis is steroids. Typical doses of 40–60 mg prednisolone are used, being trailed off over 3 months.[10] If amiodarone cannot be stopped, then definitive treatment is usually required. This could either be by radio-iodide or subtotal thyroidectomy.[7]

Table 3: Differentiation of type-1 and type-2 amiodarone-induced thyrotoxicosis

	Type 1	Type 2
Underlying thyroid disease	Yes	No
Ultrasound appearance	Large and hypoechoic May be nodular	Normal
Radioactive iodine uptake	Normal or increased	Decreased
Is stopping amiodarone effective?	Rarely	Often
Pharmacotherapy*	Carbimazole (6–9 months while amiodarone is cleared)	Prednisolone (3-month course)
Definitive treatment in refractory cases or if amiodarone cannot be stopped	Radioactive iodine or subtotal thyroidectomy	

*May be successful when amiodarone can be stopped

In practice, differentiating between type 1 and type 2 amiodarone-induced thyrotoxicosis is difficult (Table 3). Combined with the fact that many patients go on to require definitive treatment, such as surgery or radioablation, it is recommended that the care of patients with amiodarone-induced thyrotoxicosis involves an endocrinologist.[6]

Summary

Amiodarone is a commonly prescribed drug, especially in the older population. It is important health professionals are aware of and competent in managing its side-effects. The high incidence of thyroid dysfunction merits a high index of suspicion when monitoring these patients. The decision of whether to stop amiodarone in those with thyroid dysfunction should be made on an individual basis. The presence of thyroid autoantibodies suggests underlying thyroid dysfunction and a need for definitive treatment. Due to difficulties in differentiating between type-1 and type-2 amiodarone-induced thyrotoxicosis, the care of these patients should involve an endocrinologist. However, it is useful for all physicians to be competent in the monitoring and assessment of thyroid dysfunction in those patients taking long-term amiodarone.

I have no conflict of interest.

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