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Monitoring thyroid function during amiodarone use

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Abstract

Amiodarone is an antiarrhythmic drug used to treat cardiac tachyarrhythmias. It has many adverse effects, with thyroid dysfunction one of the most notable. Through various mechanisms, both thyrotoxicosis and hypothyroidism can occur secondary to amiodarone therapy. There are two types of amiodarone-induced thyrotoxicosis: type 1 occurs in those with pre-existing thyroid disease and is treated with thionamide, whereas type 2 occurs in those without and is treated with glucocorticoids. Patients with amiodarone-induced hypothyroidism may be given levothyroxine to replace thyroid hormone, but in some cases, the appropriate management may be cessation of amiodarone.

Key words: Amiodarone; Hypothyroidism; Thyroid; Thyroxine; Thyrotoxicosis

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Introduction

Amiodarone is commonly used in the treatment of a variety of arrhythmias including ventricular and supraventricular tachycardias. While it is widely regarded as an effective agent for cardiovascular disease, it has a notorious side-effect profile, including thyroid dysfunction. Thus, active monitoring is vital to identify and treat active disturbance of thyroid function.

Mechanism of action

Amiodarone is the most commonly used antiarrhythmic agent worldwide (Florek and Girzadas, 2023). It is well established in the treatment of both acute and chronic ventricular and supraventricular tachyarrhythmias. Amiodarone is in class III of the Vaughan Williams classification, causing prolongation of the action potential. Class III agents bind and block voltage-gated potassium channels during phase 3 of the cardiac action potential, delaying repolarisation and hence increasing the effective refractory period (Klabunde, 2023). Thus, cardiac myocyte excitability is reduced, stopping re-entry circuits or ectopic foci from perpetuating a tachyarrhythmia.

Clinical indications

One of the most common indications for amiodarone is in the treatment of atrial fibrillation with fast ventricular response, because amiodarone can slow the ventricular rate by prolonging the cardiac action potential and is often used in haemodynamically unstable patients (Florek and Girzadas, 2023). Moreover, it acts as a pharmacological cardioversion agent, to restore and maintain sinus rhythm, in both the acute and chronic setting. The advantage of amiodarone is that it is appropriate to use in patients with congestive cardiac failure, as it has relatively insignificant negative inotropic activity, without the vasodilatory effects seen in other rate-controlling antiarrhythmic drugs (Van Herendael and Dorian, 2010).

Other common uses of amiodarone include the treatment of supraventricular tachyarrhythmias and ventricular arrhythmias – specifically ventricular fibrillation and ventricular tachycardia. It is also part of the adult cardiac arrest resuscitation algorithm in the UK when treating patients with shockable arrhythmias (Soar et al, 2021).

Pathophysiology of amiodarone-induced hypothyroidism

Patients taking amiodarone are at risk of both thyrotoxicosis and hypothyroidism, with hypothyroidism about twice as common (Florek and Girzadas, 2023).

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The significant side-effect profile related to the thyroid gland can be explained by the remarkable similarities in the structure of amiodarone and thyroid hormones, and the high iodine content of amiodarone. Amiodarone contains two atoms of iodine per molecule, translating to approximately 37.5% of organic iodine by weight, of which 10% is converted to free iodine. This is then stored in various parts of the body including the lungs, liver and myocardium (Loh, 2000). Therefore, the total amount of free iodine generated after a standard maintenance dose of amiodarone is far greater than recommended levels, increasing the potential for thyroid dysfunction in those taking the drug. This is perpetuated by the long half-life of amiodarone (2–3 months), prolonging its effects even after it has been withdrawn (Loh, 2000).

Typically, the thyroid profile of patients commenced on amiodarone has a decreased serum level of triiodothyronine, increased serum level of thyroxine (and reverse triiodothyronine if measured) and normal or mildly raised serum level of thyroid-stimulating hormone. While the effects of thyroid dysfunction can in part be explained by the excess iodine levels, intrinsic drug factors of amiodarone are also instrumental in this, namely inhibition of iodothyronine 5'-deionidase (Trohman et al, 2019). This enzyme metabolises thyroxine to its active metabolite triiodothyronine via the removal of iodine atoms, leading to a relative reduction in triiodothyronine compared to thyroxine from usual serum levels. Inhibition of 5'-deionidase also causes reduced clearance of reverse triiodothyronine, thereby elevating its levels (Kucharczyk et al, 2006; Trohman et al, 2019).

The Wolff–Chaikoff effect is an autoregulatory mechanism of the thyroid gland that blocks excess synthesis of thyroid hormone in response to rapidly rising levels of circulating iodine. In a normal thyroid gland, this blockade is eventually evaded by reducing the amount of iodine transported intracellularly to a level inadequate to maintain the Wolff–Chaikoff effect. This leads to an escape phenomenon which increases production of thyroid hormone. However, in patients who are taking amiodarone, suppression by the Wolff–Chaikoff effect may persist as a result of excess levels of iodine leading to clinically significant hypothyroidism (Bogazzi and Martino, 2018).

Risk factors associated with the development of amiodarone-induced hypothyroidism are thought to include increasing age, diabetes mellitus, elevated levels of baseline thyroid-stimulating hormone and the presence of thyroid autoantibodies. Moreover, people living in iodine-sufficient areas, such as Japan and places where there is a prominent fish and seafood influence in the diet, are at a higher risk of developing amiodarone-induced hypothyroidism (Kinoshita et al, 2016).

Treatment of amiodarone-induced hypothyroidism

Amiodarone-induced hypothyroidism may manifest both early on and much later during treatment with amiodarone, with symptoms as expected from other causes of hypothyroidism. This may be transient or may persist if there is an underlying thyroid disorder. Ideally, treatment should be the discontinuation of amiodarone, but if this is not appropriate then levothyroxine may be given alongside amiodarone (Loh, 2000).

Amiodarone-induced thyrotoxicosis

There are two types of amiodarone-induced thyrotoxicosis, which may be difficult to distinguish between clinically.

Amiodarone-induced thyrotoxicosis type 1 occurs as a result of iodine overload of an abnormal thyroid gland. Such abnormalities include single autonomous nodules, multinodular goitre or latent Graves' disease (Loh, 2000). This leads to excess synthesis of thyroid hormone and subsequent thyrotoxicosis. Treatment is with thionamide drugs, such as carbimazole, in some instances, combined with sodium perchlorate, which increases the sensitivity of the thyroid gland to the antithyroid agent (Macchia and Feingold, 2022). After treatment with antithyroid agents to restore euthyroidism, definitive treatment should be considered – either thyroidectomy or radioiodine therapy.

In contrast, amiodarone-induced thyrotoxicosis type 2 occurs in patients with a previously normal thyroid gland. Amiodarone causes a destructive thyroiditis that results from damage

to the thyroid gland and release of preformed thyroid hormones. It may be self-limiting, but treatment includes corticosteroids, such as prednisolone. Cases are usually followed up without the need for any further treatment (Loh, 2000). Type 2 occurs more commonly than type 1 in most countries (Macchia and Feingold, 2022). It is important to remember that typical symptoms of thyrotoxicosis such as weight loss, heat intolerance and diarrhoea may not be present, as these can be masked by the beta-blocking effects of amiodarone (Florek and Girzadas, 2023).

Differentiating between the two types of thyrotoxicosis can be challenging, and there is a 'mixed' type with overlap features of both. Colour flow Doppler ultrasonography may be useful to differentiate between the two forms, with type 1 showing increased vascularity and type 2 showing reduced or absent vascularity. Antithyroid peroxidase antibodies are more likely to be positive in type 1 and negative in type 2, but these are not diagnostic (Bartalena et al, 2018). Radioisotope imaging is sometimes used. Regardless of the cause, timely treatment to restore euthyroidism for both types of amiodarone-induced thyrotoxicosis is important, as patients are at an increased risk of adverse cardiac events (Narayana et al, 2011). In clinical situations where it is not possible to distinguish between types despite investigations, a dual approach to management is sometimes used with both steroid and antithyroid therapy provided together. Response to treatment can guide further therapy (Chua and Mok, 2020) (Figure 1).

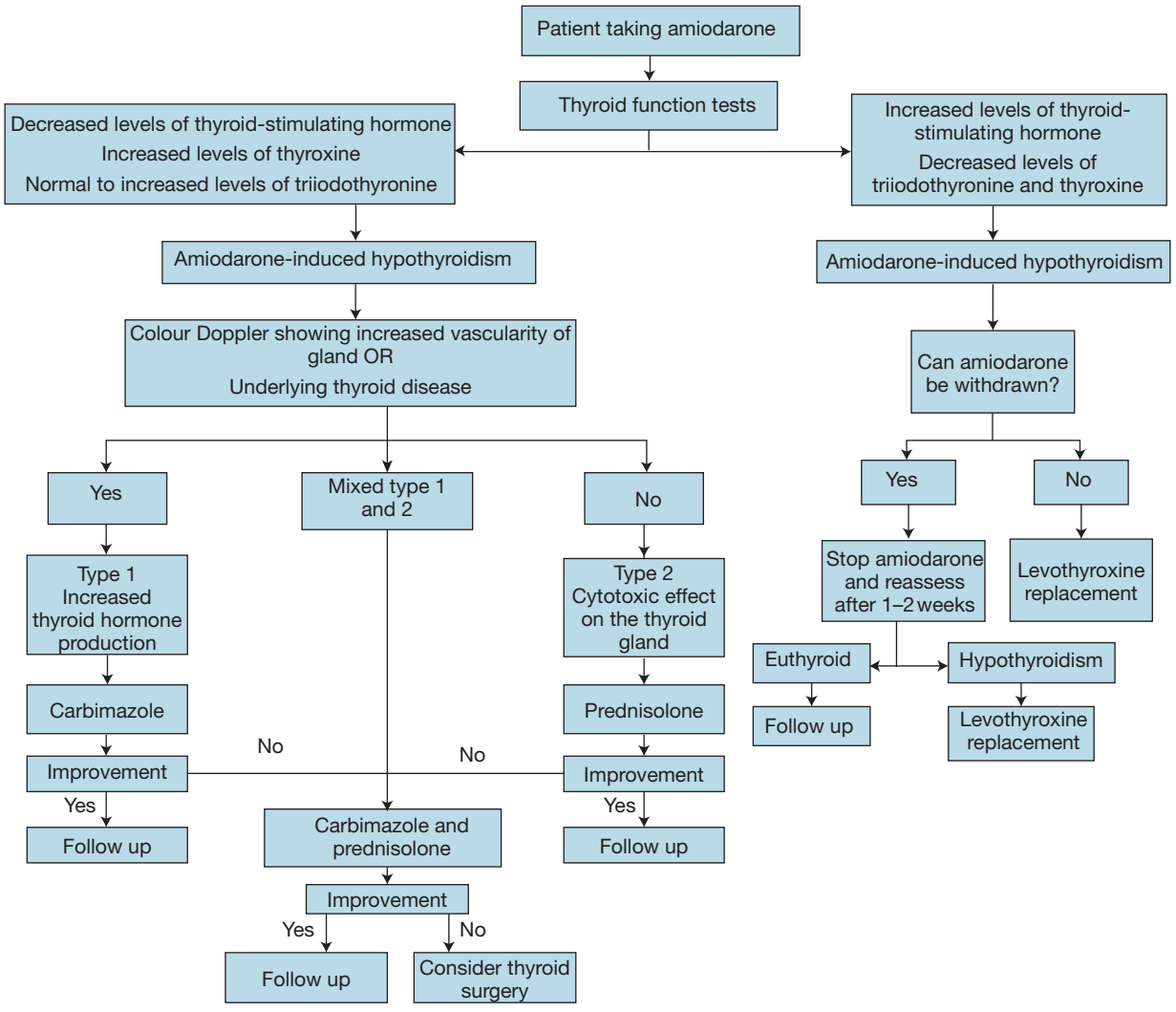

Figure 1. Algorithm for the management of amiodarone-induced thyroid dysfunction. Adapted from Bartalena et al (2018) and Ylli et al (2021).

Current guidelines for monitoring

Current National Institute for Health and Care Excellence (2023) guidelines advise that amiodarone should only be started in secondary care. Thyroid function tests should be measured at baseline and then every 6 months. If any abnormalities are detected, specialist advice should be sought. Before starting treatment, a chest radiograph should be performed. Liver function tests and urea and electrolytes should be measured every 6 months, and an electrocardiogram should be done at baseline and then every 12 months to assess for any conduction abnormalities. A repeat thyroid function test should be checked 12 months after discontinuation of therapy (National Institute for Health and Care Excellence, 2023).

Personalised decision making

Amiodarone remains an effective and desirable antiarrhythmic agent for a range of cardiovascular conditions. Given its superiority over other antiarrhythmic agents, for example in severe left ventricular systolic dysfunction (Van Erven and Schalij, 2010), it is unlikely to be phased out of medical practice in the short term and so the decision to continue its use, in view of the known side effects, needs to be evaluated on a case-by-case basis. The decision to stop amiodarone is fraught with challenges, especially when being used to treat life-threatening arrhythmias. Emergency thyroidectomies for amiodarone-induced thyrotoxicosis have been performed in the past (Kotwal et al, 2018). A multidisciplinary approach with patient involvement in balancing the risks and benefits of continued amiodarone therapy is vital for effective management of the thyroid dysfunction.

Conclusions

Clinicians should be aware of baseline thyroid function status before amiodarone use and adhere to the serial monitoring of thyroid function during treatment, as it is a commonly used drug. Clear handover should be made of the monitoring requirements when transferring care back to the primary care physician.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

Key points

- Amiodarone is an antiarrhythmic drug that may be associated with thyroid dysfunction, either amiodarone-induced thyrotoxicosis or amiodarone-induced hypothyroidism.
- There are two types of amiodarone-induced thyrotoxicosis, with type 1 occurring in patients with pre-existing thyroid gland abnormalities and type 2 occurring in those with a previously normal thyroid gland.
- Treatment of amiodarone-induced thyrotoxicosis type 1 includes carbimazole, which may then be followed by thyroidectomy. In contrast, type 2 is treated with corticosteroids.
- Treatment of amiodarone-induced hypothyroidism involves either the discontinuation of amiodarone or the addition of levothyroxine, depending on the circumstances.
- For patients taking amiodarone, thyroid function tests should be measured at baseline and then every 6 months thereafter.

Curriculum checklist

This article addresses the following requirements from the general internal medicine training curriculum:

- Communicates effectively and is able to share decision making, while maintaining appropriate situational awareness, professional behaviour and professional judgement
- Managing patients in an outpatient clinic, ambulatory or community setting, including management of long-term conditions
- Managing medical problems in patients in other specialties and special cases.

References

Bartalena L, Bogazzi F, Chiovato L et al. European Thyroid Association (ETA) guidelines for the management of amiodarone-associated thyroid dysfunction. Eur Thyroid J. 2018;7(2):55–66. https://doi.org/10.1159/000486957

Bogazzi F, Martino E. Amiodarone and thyroid. Encyclopedia Endocrine Dis. 2018;782–786. https://doi.org/10.1016/b978-0-12-801238-3.96000-8

Chua MWJ, Mok SF. Amiodarone induced thyrotoxicosis and treatment complications in a man with cyanotic congenital heart disease: a case report. Front Cardiovasc Med. 2020;7:574391. https://doi.org/10.3389/fcvm.2020.574391

National Institute for Health and Care Excellence. Amiodarone - not initiated in primary care. 2023. https://cks.nice.org.uk/topics/atrial-fibrillation/prescribing-information/amiodarone-not-initiated-in-primary-care/ (accessed 29 December 2023)

Florek JB, Girzadas D. Amiodarone. 2023. Treasure Island (FL): StatPearls Publishing

Kinoshita S, Hayashi T, Wada K et al. Risk factors for amiodarone-induced thyroid dysfunction in Japan. J Arrhythmia. 2016;32(6):474–480. https://doi.org/10.1016/j.joa.2016.03.008

Klabunde K. Class III antiarrhythmics (potassium channel blockers). 2023. https://www.cvpharmacology.com/antiarrhy/potassium-blockers (accessed 29 December 2023)

Kotwal A, Clark J, Lyden M et al. Thyroidectomy for amiodarone-induced thyrotoxicosis: mayo clinic experience. J Endocrine Soc. 2018;2(11):1226–1235. https://doi.org/10.1210/js.2018-00259

Kucharczyk P, Michałkiewicz D, Kucharczyk A. [The effects of amiodaron on the thyroid function]. Pol Merkur Lekarski. 2006;21(121):86–89

Loh K-C. Amiodarone-induced thyroid disorders: A clinical review. Postgraduate Med J. 2000;76(893):133–140. https://doi.org/10.1136/pmj.76.893.133

Macchia PE, Feingold KR. Amiodarone induced thyrotoxicosis. 2022. https://www.ncbi.nlm.nih.gov/books/NBK279030/ (accessed 16 January 2024)

Narayana SK, Woods DR, Boos CJ. Management of amiodarone-related thyroid problems. Ther Adv Endocrinol Metab. 2011;2(3):115–126. https://doi.org/10.1177/2042018811398516

National Institute for Health and Care Excellence. Amiodarone - not initiated in primary care. 2023. https://cks.nice.org.uk/topics/atrial-fibrillation/prescribing-information/amiodarone-not-initiated-in-primary-care/ (accessed 29 December 2023)

Soar J, Deakin C, Nolan J et al. Adult advanced life support guidelines. 2021. https://www.resus.org.uk/library/2021-resuscitation-guidelines/adult-advanced-life-support-guidelines#references (accessed 29 December 2023)

Trohman RG, Sharma PS, McAninch EA et al. Amiodarone and thyroid physiology, pathophysiology, diagnosis and management. Trends Cardiovasc Med. 2019;29(5):285–295. https://doi.org/10.1016/j.tcm.2018.09.005

Van Erven L, Schalij MJ. Amiodarone: an effective antiarrhythmic drug with unusual side effects. Heart. 2010;96(19):1593–1600. https://doi.org/10.1136/hrt.2008.152652

Van Herendael H, Dorian P. Amiodarone for the treatment and prevention of ventricular fibrillation and ventricular tachycardia. Vasc Health Risk Manag. 2010;6:465–472. https://doi.org/10.2147/vhrm.s6611

Ylli D, Wartofsky L, Burman KD. Evaluation and treatment of amiodarone-induced thyroid disorders. J Clin Endocrinol Metabolism. 2021;106(1):226–236. https://doi.org/10.1210/clinem/dgaa686