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Amiodarone-induced thyrotoxicosis

CLINICAL REVIEW

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We see an increasing number of patients with amiodarone-induced thyrotoxicosis. This condition can be treated pharmacologically, but treatment over several months may give rise to adverse reactions. In most cases we recommend that amiodarone therapy be continued despite newly detected thyrotoxicosis. Particularly in cases of heart failure, one should not wait too long before considering

thyroidectomy. Treatment of amiodarone-induced thyrotoxicosis must be delivered with close collaboration between endocrinologist and cardiologist.

Amiodarone is the most potent drug available against cardiac tachyarrhythmias, but it frequently gives rise to adverse reactions that may affect different organ systems. The drug is used for life-threatening ventricular arrhythmias, to prevent episodes and reduce the risk of shocks from an implantable cardioverter defibrillator (ICD). It can also be used in patients with disabling atrial fibrillation to maintain normal sinus rhythm (rhythm control) if other drugs are inadequate or cannot be used. We have treated many patients with amiodarone-induced thyrotoxicosis and have the impression that the incidence is increasing. In accordance with this, data from the Norwegian Prescription Registry for the period 2010–2019 revealed a 42 % increase in dispensed daily doses of amiodarone (1). Practically the entire increase occurred in the group of atrial fibrillation-related diagnoses (atrial fibrillation, atrial flutter and atypical atrial flutter, diagnostic codes I48 in the ICD-10-classification and K78 in ICPC), while consumption for ventricular arrhythmias (I47/K79 and I49/K80) was virtually unchanged. In 2019, atrial fibrillation-related dispensing accounted for 75 % of amiodarone consumption (1). Knowledge about amiodarone-induced thyrotoxicosis is largely based on clinical experience with individual patients or small registry studies (2, 3). Based on our own experience and relevant literature searches, we provide an overview of the clinical picture, pathophysiology, diagnostics, and treatment of the condition.

The clinical picture

Box 1 contains three case histories that illustrate different courses of amiodarone-induced thyrotoxicosis. Hormonal test results at the time of diagnosis are shown in Table 1.

Box 1 Three case histories that illustrate different courses of amiodarone-induced thyrotoxicosis.

At Akershus University Hospital, prednisolone is generally administered once daily (patients 1 and 2), but where the daily dosage exceeds 20 mg, it is sometimes divided into two doses (patient 3). Dronedarone (Multaq) is an antiarrhythmic drug derived from amiodarone, but without iodine and less potent than amiodarone.

Patient 1

A young man with arrhythmogenic right ventricular cardiomyopathy (ARVC) received an implantable cardioverter-defibrillator (ICD) in his teens. Amiodarone therapy was started due to frequent ventricular tachycardias and shocks from the ICD despite treatment with metoprolol succinate and sotalol.. After seven years, a routine check-up revealed probable amiodarone-induced thyrotoxicosis (Table 1). The patient had noted a higher resting pulse rate,

increased heat intolerance and restlessness in recent weeks. An ultrasound scan revealed a normal-sized, homogeneous thyroid gland with slight hypervascularisation. The patient was treated with 40 mg prednisolone and 20 mg x 2 carbimazole daily, tapered after clinical and biochemical response. Amiodarone was continued. The thyroid hormone tests normalised after three months. Three years later biochemical analyses again revealed hyperthyroidism requiring prednisolone and carbimazole therapy. High-dose steroid therapy had to be maintained for 2.5 months. The total treatment time was 5 months, after which he underwent a thyroidectomy. Three years later the patient was clinically stable and arrhythmia-free on low-dose amiodarone (600 mg per week) and levothyroxine.

Patient 2

A man in his seventies was prescribed amiodarone because of disabling atrial fibrillation and atypical atrial flutter with rapid ventricular rate despite two catheter ablation procedures. Dronedarone therapy was not sufficient, and he suffered an early relapse after cardioversion. After three months on amiodarone, he developed symptomatic thyrotoxicosis with nocturnal sweating. An ultrasound scan of the thyroid revealed hypoechoic lesions in both lobes and a moderately increased blood flow rate. Amiodarone was continued, and the patient was treated with carbimazole 10 mg x 3 and prednisolone 40 mg daily. However, a few weeks later he developed bone marrow suppression (agranulocytosis) secondary to the carbimazole therapy, with a fall in leukocyte concentration to 1.8×10^9/L (reference range $3.5–10.0 \times 10^9$) and neutrophil granulocytes to 0×10^9/L ($1.5–7.3 \times 10^9$). Both carbimazole and amiodarone were discontinued, and the patient underwent a thyroidectomy. Some weeks later the patient underwent a third ablation procedure for ongoing atypical atrial flutter with 2:1 conduction and a ventricular rate of 110 beats/min despite beta-blockade. Following successful treatment of a macroreentrant tachycardia in the roof of the left atrium and reisolation of the right pulmonary veins, he has subsequently been free of arrhythmia without amiodarone, but with levothyroxine as a substitute.

Patient 3

A man in his forties suffered severe post-infarction heart failure after a major ST elevation myocardial infarction, despite primary percutaneous coronary revascularisation. He received an ICD because of ventricular tachycardia following an aortocoronary bypass-graft operation. Amiodarone therapy was started because of rapid atrial fibrillation and inappropriate shocks from the ICD. After three years on amiodarone, he developed hyperthyroidism (Table 1). An ultrasound scan of the thyroid was not performed. Thyroid scintigraphy with $^{99\,m}$Tc pertechnetate showed no uptake, but $^{99\,m}$Tc sestamibi revealed slight uptake in both lobes. The patient was treated with carbimazole 15 mg x 3 and prednisolone 20 mg x 2 daily, which were tapered and discontinued after six months. The amiodarone therapy was discontinued within two months, but one year later had to be resumed due to recurring ventricular tachycardias and ICD shocks. The patient underwent a total of three catheter ablation procedures targeting the infarct zone in the left ventricle, but without achieving permanent control of the arrhythmias. An attempt was made to stop the amiodarone treatment, but it had to be resumed. The patient was assessed several times for

a heart transplant, and after the third ablation procedure he was formally accepted on the waiting list for a new organ. However, he had again developed thyrotoxicosis, treated with carbimazole 15 mg x 3 and methyl prednisolone 16 mg x 2 daily. Secondary to this, he developed myopathy and diabetes. A thyroidectomy was scheduled, but the patient died before the operation could be performed. Nineteen years had passed since the patient's first myocardial infarction. The cause of death was advanced post-infarction heart failure, but we cannot exclude the possibility that thyrotoxicosis contributed to exacerbation of both the ventricular arrhythmias and the heart failure.

Table 1

Thyroid function tests at time of diagnosis for our patients. Patients 1 and 3 had two episodes of amiodarone-induced thyrotoxicosis several years apart, designated -1 and -2 here. TSH = thyroid-stimulating hormone, F-T4 = free thyroxine, F-T3 = three triiodothyronine, TRAB = TSH receptor antibody, anti-TPO = thyroid peroxidase antibodies. The laboratory's reference range is given in brackets in the first column.

Test	Patient 1 - 1	Patient. 1 - 2	Patient 2	Patient 3 - 1	Patient 3 - 2
TSH, mIU/L (0.5–3.6)	0.01	< 0.01	0.02	< 0.02	0.01
F-T4, pmol/L (8.0–21)	72	75	42	56	52
F-T3, pmol/L (2.8–7.0)	10	11.3	4.7	12	6.8
TRAB, IU/L (< 1.8)	< 0.9		< 1.1	< 0.9	< 1.1
Anti-TPO, IU/L (< 35)	2		< 9	1	< 9

Pathophysiology

Amiodarone is an antiarrhythmic drug that mainly affects potassium channels and prolongs the repolarisation phase of the action potential (Class III effect). However, amiodarone is also a multi-ion channel inhibitor that affects conduction velocity (Class I effect), has a certain beta-blocking effect and a weak calcium antagonistic effect. Amiodarone is stored in adipose tissue and eliminated via the liver with a half-life of 50–100 days (4). After the discontinuation of maintenance dosing, the substance may still be present in the body after a year (five half-lives). A normal 200 mg maintenance dose contains the equivalent of 6 mg of free iodine. Recommended dietary iodine intake is 50–150 µg daily, depending on age (5). The practical use and adverse reaction profile of amiodarone have been described in the journal *Hjerteforum* (1, 6).

Because of the high iodine content, amiodarone often affects the thyroid gland. In the first month after treatment start, one often sees a 20–40 % increase in the concentration of free thyroxine (F-T4), a 30 % reduction in free

triiodothyronine (F-T3) and a slight increase in thyroid-stimulating hormone (TSH) which may exceed the upper normal limit (7). After three to six months, a new equilibrium is established with a normal concentration of TSH, F-T4 slightly increased or in the upper normal range and F-T3 in the lower normal range (7). A treatment plan should therefore not be changed because of such early fluctuations in hormone concentrations.

In areas with an adequate amount of dietary iodine, amiodarone-induced hypothyroidism is most common, while in areas with an iodine deficiency amiodarone-induced hyperthyroidism is seen more frequently (i.e., amiodarone-induced thyrotoxicosis) (8). This has been explained by an increased incidence of non-toxic nodular goitre in areas with low dietary iodine, which may make patients more sensitive to exogenous iodine (7). Milk and white saltwater fish are the most important sources of iodine in the Norwegian diet. Ordinary table salt sometimes has added iodine, but the quantity has little effect on our iodine intake. Reduced milk consumption means that iodine deficiency has again become relevant in Norway, particularly for those who do not eat white fish or fish products (5). Given a growing iodine deficiency, it is to be expected that amiodarone-induced thyrotoxicosis will become more prevalent.

There are two main types of amiodarone-induced thyrotoxicosis. Type I is due to increased synthesis of thyroid hormone, while type II is caused by increased release (leakage) from follicular cells due to destructive thyroiditis. Sometimes mixed pictures are seen. Type I tends to occur in patients who already have a nodular goitre or latent Grave's disease (hyperthyroidism), while type II arises without previous thyroid disease. Studies indicate that the prevalence of amiodarone-induced thyrotoxicosis is 3–5 % among patients treated with amiodarone in areas with adequate iodine intake (8), and that the risk increases with the cumulative dose of amiodarone. The onset of type I often occurs soon after the start of amiodarone treatment (median 3.5 months), type II later (median 30 months). (9). Type II in particular may manifest itself after the amiodarone treatment has been discontinued. We view patient 1 as having a type II condition since it resolved despite further amiodarone treatment, but an ultrasound scan showed increased vascularisation that might indicate a mixed type. Patient 2 probably had Type 1 amiodarone-induced thyrotoxicosis, as indicated by an escalating thyrotoxicosis despite initial steroid treatment, response to an increased carbimazole dose, thyroid nodules and moderately increased blood flow velocity on the ultrasound, and symptom onset within three months of the initiation of amiodarone therapy. Patient 3 may have had the mixed type the first time (findings of $^{99\,m}$Tc sestamibi scintigraphy) and type II the second time. Differentiation may be difficult, but some evidence is compiled in Table 2 (modified from (2)).

Table 2

Features of type I and type II amiodarone-induced thyrotoxicosis (modified from (2)). Typical findings may be absent, and mixed types occur. Colour-flow Doppler sonography is considered by many to be the best method for distinguishing between type I and type II amiodarone-induced thyrotoxicosis, but the method requires

specialist experience. Ordinary thyroid scintigraphy (99 mTc pertechnetate) correlates with iodine uptake. Technetium-sestamibi scintigraphy shows metabolically active tissue, but the test may be inconclusive.

Variable	Type I	Type II
Thyroid tests	Suppressed TSH and high F-T4, high or normal FT3	Suppressed TSH and high F-T4, F-T3 high or normal
Underlying thyroid disorder	Yes	No
Pathogenesis	Iodine-induced hyperthyroidism, increased production	Destructive thyroiditis, leakage
Time after starting amiodarone	Short (median 3 months)	Long (median 30 months)
Thyroid antibodies	May be present	Absent
Thyroid ultrasound	Diffuse or nodular goitre	Normal gland or small goitre
Colour-flow Doppler sonography	Increased vascularisation	Low or no vascularisation
$^{99\,m}$Tc sestamibi scintigraphy	High uptake	Low/lack of uptake
$^{99\,m}$Tc sestamibi pertechnetate scintigraphy	Low/normal/increased uptake	No uptake
Treatment	Thyrostatics (thionamides)	Glucocorticoids
Spontaneous remission	No	Possible
Prognosis if amiodarone is continued	Persistent hyperthyroidism	Prolonged hyperthyroidism, normalisation or transition to hypothyroidism.
Prognosis if amiodarone is discontinued	Thyrotoxicosis may resolve in the long term, but amiodarone has a long half-life	The thyrotoxicosis may go into remission, but may also arise many months after the discontinuation of amiodarone

Diagnosis of amiodarone-induced thyrotoxicosis

The diagnosis is most frequently based on routine blood tests which show suppressed TSH, elevated F-T4 and normal or elevated F-T3 in patients who use amiodarone.

Patients may have clinical symptoms of hyperthyroidism in the form of weight loss, bouts of sweating, shivering and palpitations, but the clinical symptoms may be modest at the time of diagnosis, particularly if F-T3 has not risen appreciably. Thyroid antibodies may be present in type I. We recommend an ultrasound scan of the thyroid gland with colour-flow Doppler sonography, which sometimes helps to distinguish between types I and II (Table 2).

Ordinary thyroid scintigraphy ($^{99\,m}$Tc pertechnetate) to estimate iodine uptake is of little benefit because the gland is fully saturated with iodine. Technetium-sestamibi scintigraphy, which shows metabolically active tissue, can sometimes distinguish between types I and II (Table 2) (10), but the result is often inconclusive (V. Jøraholmen, Nuclear Medicine at Akershus University Hospital, personal communication).

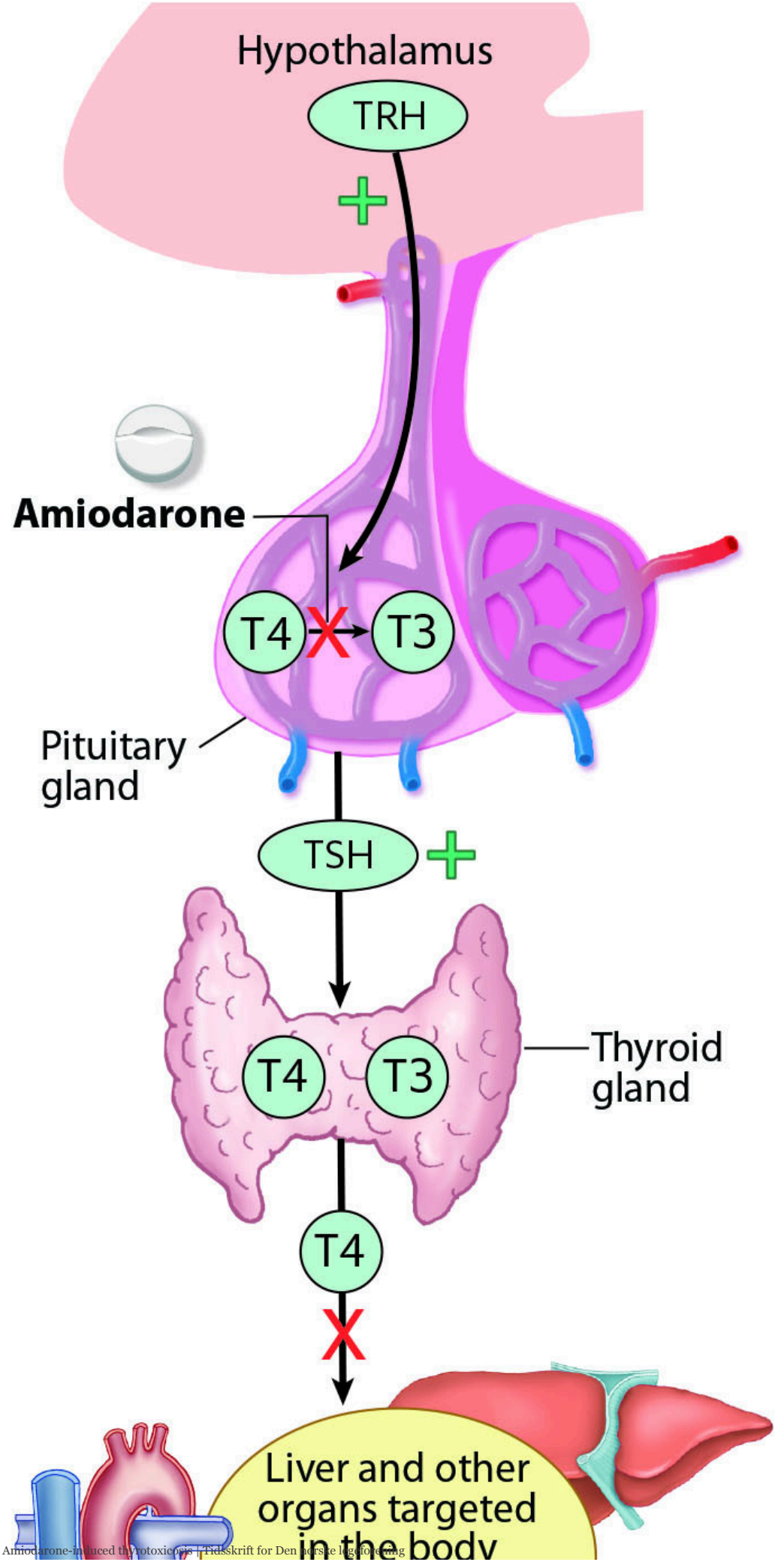
Treatment of amiodarone-induced thyrotoxicosis

The initial treatment consists of thyrostatics (carbimazole, Neo-Mercazole) and/or steroids. Carbimazole acts primarily against increased hormone production (type I), while steroids act against leakage of hormones due to destructive thyroiditis (type II). Initially, all our patients received combination treatment as recommended for those with pronounced hyperthyroidism and reduced cardiac function (3). Sometimes the response to the initial treatment may indicate the mechanism underlying the condition. If the patient's thyroid hormone levels fall within a week or two, this indicates that high-dose steroids are effective against leakage (type II) (11). Carbimazole treatment can then be tapered more rapidly. Often both drugs need to be used in high doses for several months, and this may cause adverse reactions such as agranulocytosis because of carbimazole, or myopathy or diabetogenic effect due to steroid treatment (12). In patients with heart failure, it may be advantageous to use methyl prednisolone instead of prednisolone because of its weaker mineral corticoid effect resulting in less fluid retention (3). It is a dilemma that we may overtreat some patients with amiodarone-induced thyrotoxicosis with few clinical symptoms and without an elevated F-T3 level, but it is still unclear whether watchful waiting for a spontaneous resolution is adequate (13).

Radioactive iodine therapy is not possible in the acute phase of amiodarone-induced thyrotoxicosis, as the thyroid is saturated with iodine and no further uptake can be achieved. Therefore, the alternative to pharmacological treatment is surgical thyroidectomy. This entails a risk of complications related to general anaesthesia, unintentional nerve damage with vocal cord palsy or damage to the parathyroid glands with hypocalcaemia, and thyroidectomy is only indicated in exceptional cases. However, patients with heart failure in particular have a low tolerance for high-dose steroids or being hyperthyroid over a prolonged period. One should therefore not wait too long before considering thyroidectomy for these patients (14). The thyrotoxicosis ought to be under control prior to surgery. If initial treatment has not yielded sufficient effect, Lugol's solution can be used (iodine-potassium iodide 5 %) (15). Preoperative therapeutic plasmapheresis may also be an option (16).

When the diagnosis amiodarone-induced thyrotoxicosis is made, one must decide whether to stop or continue the amiodarone therapy (17). Usually, treatment is initiated because of life-threatening or disabling heart rhythm disturbances. As amiodarone has a long half-life, discontinuing the drug has little immediate effect on the iodine burden. However, patients will be less protected against arrhythmia if the drug is discontinued, and thyrotoxicosis per se lowers the arrhythmia threshold for both atrial fibrillation and ventricular

tachycardia. Amiodarone attenuates the clinical symptoms of thyrotoxicosis by inhibiting the conversion of thyroxine (T4) to triiodothyronine (T3) (18) and acts at several levels in the body (Figure 1). The heart primarily has triiodothyronine receptors, thus most cardiac symptoms in thyrotoxicosis are mediated via T3. Amiodarone also has a certain beta-blocking effect. Paradoxically, stopping amiodarone therapy may both accentuate the clinical symptoms of thyrotoxicosis and make the patient more prone to arrhythmias. In most cases, our advice is *not* to stop the therapy immediately. The original indication can be reconsidered when the thyroid function is under control. If amiodarone therapy can be discontinued, but the nature of the cardiac disease suggests a high probability that the drug may be needed again later, prophylactic radioactive iodine therapy may be justified when the patient has measurable radioactive iodine uptake (19).



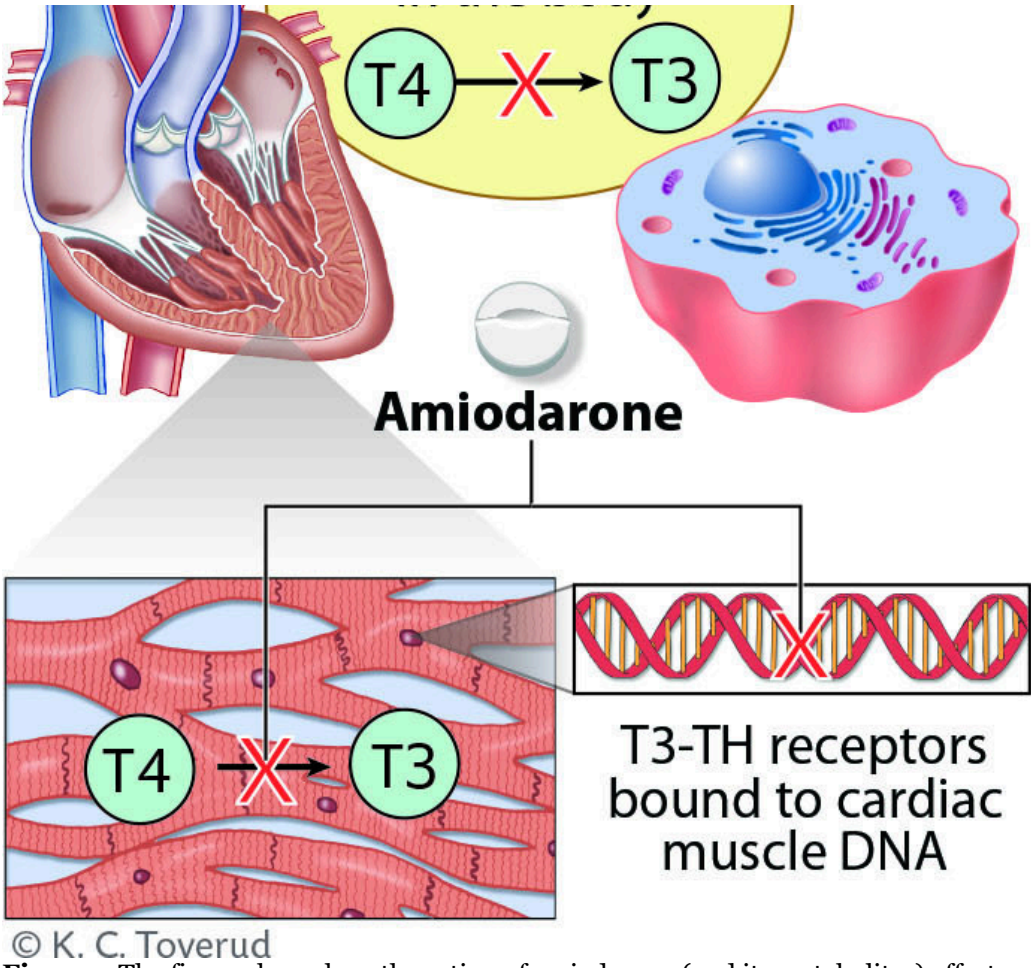


Figure 1 The figure shows how the action of amiodarone (and its metabolites) affects the metabolism of thyroid hormones at several levels in the body, and to a certain extent counteracts the effects of the high level of circulating thyroxine (T4) due to amiodarone itself, with its high iodine content. Amiodarone inhibits the conversion of T4 to T3 (triiodothyronine) in the pituitary gland, liver and other organs targeted by thyroid hormone (marked with red crosses). In the liver there is reduced uptake of T4 from the blood. In the myocardial cells, amiodarone acts on two levels: inhibiting the conversion of T4 to T3, and inhibiting the interaction between T3 thyroid hormone receptor complex and cardiac muscle DNA. TRH = thyrotropin-releasing hormone, TSH = thyroid-stimulating hormone, TR = thyroid hormone.

Amiodarone consumption in Norway has increased by 42 % in the last ten years. This increase is due to atrial fibrillation-related diagnoses (1). During the same period, catheter ablation of atrial fibrillation has increased. The prevalence of atrial fibrillation is increasing because of the age distribution of the population and lifestyle-related risk factors (20). More patients want heart rhythm control rather than heart rate control. The indication for using amiodarone for long-term rhythm control was recently upgraded in the 2020 European Society of Cardiology atrial fibrillation guidelines. The recommendation used to be Class IIa, evidence level C, but is now Class I, evidence level A, admittedly still with the notion that because of the adverse reaction profile, other antiarrhythmic agents should be considered first (20). It is a matter for concern if the upgrading of the recommendation for amiodarone leads to increased use and a lower threshold for prescribing this drug.

Treatment that was intended to be temporary, until ablation could be performed, often becomes prolonged over many months. One should therefore not be too eager to use this admittedly most effective, but also most toxic, drug.

Thyroid function tests (TSH, F-T4 and F-T3) must be controlled regularly in all patients who are treated with amiodarone. Testing is recommended at the start of treatment, after three months, and then semi-annually (4). Cardiologist and GP must reach agreement on the responsibility for testing, and it is natural to involve an endocrinologist if amiodarone-induced thyrotoxicosis is detected. Cardiologist and endocrinologist must cooperate on the further management of both hyperthyroidism and cardiac rhythm disturbances. The question of thyroidectomy must be discussed in an interdisciplinary forum in which endocrinologist, cardiologist and endocrine surgeon are all involved.

Conclusion

The consumption of amiodarone for cardiac tachyarrhythmias has increased. At the same time, we have registered many patients with amiodarone-induced thyrotoxicosis. Prolonged treatment with thyrostatics and high-dose steroids may give rise to significant adverse effects. For patients with heart failure in particular, a thyroidectomy should not be postponed for too long. In most cases, amiodarone therapy should be maintained until the thyroid function is under control, and not be discontinued if the indication was life-threatening arrhythmia. We recommend establishing a national register for amiodarone-induced thyrotoxicosis in order to acquire knowledge about the scope of the problem and what is the best treatment strategy.

Patients 1 and 2 have consented to the publication of the article. The family of patient 3 have consented to the publication of the article.

The article has been peer-reviewed.

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