REVIEWS

Effects of amiodarone therapy on thyroid function

Janna Cohen-Lehman, Peter Dahl, Sara Danzi and Irwin Klein

Abstract | Amiodarone is a benzofuran derivative approved for the treatment of cardiac arrhythmias. Traditionally classified as a class III antiarrhythmic agent, amiodarone possesses electrophysiologic properties of all four Vaughan–Williams classes. This drug, however, has high iodine content, and this feature plus the intrinsic effects on the body make amiodarone especially toxic to the thyroid gland. Treatment can result in a range of effects from mild derangements in thyroid function to overt hypothyroidism or thyrotoxicosis. The diagnosis and treatment of amiodarone-induced hypothyroidism is usually straightforward, whereas that of amiodarone-induced thyrotoxicosis and the ability to distinguish between the type 1 and type 2 forms of the disease are much more challenging. Dronedarone was approved in 2009 for the treatment of patients with atrial fibrillation. As amiodarone, dronedarone is a benzofuran derivative with similar electrophysiologic properties. In contrast to amiodarone, however, dronedarone is structurally devoid of iodine and has a notably shorter half-life. In studies reported before FDA approval, dronedarone proved to be associated with significantly fewer adverse effects than amiodarone, making it a more attractive choice for patients with atrial fibrillation or flutter, who are at risk of developing amiodarone-induced thyroid dysfunction.

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Learning objectives

Upon completion of this activity, participants should be able to:
1. Describe adverse systemic effects of amiodarone.
2. Describe the characteristics of amiodarone-induced hypothyroidism.
3. Describe the presentation and management of amiodarone-induced thyrotoxicosis.
4. Identify strategies for monitoring thyroid effects of amiodarone.
5. Describe differences between amiodarone and dronedarone.

Department of Medicine, North Shore University Hospital, 350 Community Drive, Manhasset, NY 11030, USA (**J. Cohen-Lehman**, **P. Dahl**, **S. Danzi**, **I. Klein**).

Correspondence to:
I. Klein
iklein@nshs.edu

Competing interests
The authors, the Journal Editor V. Heath and the CME questions author D. Lie declare no competing interests.

Introduction

Amiodarone is an effective medication used since the 1960s to treat anginal symptoms. Since 1985, it has been approved in the USA for the management of various ventricular cardiac rhythm disturbances, including potentially lethal ventricular arrhythmias.[1] Amiodarone is a benzofuran derivative that contains two iodine atoms per molecule (accounting for 37% of its weight).[2] The drug is distributed in the liver, lungs and myocardium, and in muscle, thyroid and adipose tissue.[3–5] In addition to its desirable therapeutic effects, amiodarone causes adverse ocular, pulmonary and thyroid effects, which restrict its use in many patients. Dronedarone is a new antiarrhythmic agent, structurally and pharmacologically similar to amiodarone but with chemical modifications that may reduce the risk of organ-specific toxic effects. This Review highlights the electrophysiologic effects of amiodarone and assesses potential complications related to the thyroid gland. Furthermore, we discuss the treatment of amiodarone-induced thyroid disease and examine the current data on dronedarone, with a focus on its adverse-effect profile.

Characteristics of amiodarone
Structure
The structural formula of amiodarone closely resembles that of thyroid hormones (Figure 1) and, because of the presence of iodine atoms, amiodarone acts in the liver and pituitary gland as a thyroid hormone analog.[6] At a standard dose of 100–600 mg per day, therefore, recipients are exposed to 3–21 mg iodine per day, which

is over 35–140 times the recommended daily allowance of iodide (150 µg per day).[7]

Pharmacokinetics

The absorption of amiodarone is slow and variable, ranging from 22–80%, the latter effect usually taking place when food is ingested at the time of drug intake. The drug's bioavailability is approximately 40%. Amiodarone is very lipophilic because of the presence of an unsubstituted benzene ring (Figure 1) and, therefore, concentrates in various tissues and organs. Its large volume of distribution is estimated at about 60 l/kg body weight.[4,5] Amiodarone is dealkylated in the liver to its major active metabolite, desethylamiodarone (DEA).[7] DEA is less lipid soluble than its parent compound and, for this reason, concentrates in adipose tissue to a lesser extent, but achieves a 10–50 times higher concentration in the myocardium.[4,8] The onset of antiarrhythmic action for DEA may, however, take several days to weeks, as it relies on cumulative dose. Use of a loading dose of amiodarone can accelerate the effect. The average half-life of amiodarone is 40 days and that of DEA is 57 days, leading to a long period of effect after drug discontinuation.[7] Amiodarone is eliminated mainly via hepatic excretion; renal excretion is insubstantial.[4,5]

Amiodarone as an antiarrhythmic

Amiodarone and DEA have multiple electrophysiologic effects.[4] Traditionally viewed as a class III antiarrhythmic, according to the Vaughan–Williams classification,[8] amiodarone has the ability to inhibit myocardial Na^+,K^+-ATPase activity, thus delaying phase 3 depolarization and increasing the action potential duration and effective refractory period. Amiodarone also decreases conduction velocity by blocking Na^+ channels (class I effect), reduces the numbers of β-adrenergic receptors with a resultant antiadrenergic effect (class II effect), and suppresses Ca^{2+}-mediated action potentials (class IV effect).[4,8] Because of its multiple effects on myocytes, including atrial myocytes, amiodarone is widely used for heart-rate control in atrial fibrillation when other treatment methods are unsuccessful.[4,9] Furthermore, this drug can be used in the suppression of supraventricular and ventricular tachyarrhythmias, and ventricular tachycardia and ventricular fibrillation associated with coronary artery disease and hypertrophic cardiomyopathy.[7,10] Amiodarone also has a class IIb electrophysiologic application for the prevention of sudden cardiac death in patients who are not eligible for implantation of a cardioverter–defibrillator.[1]

Effects of amiodarone on thyroid function

Amiodarone has many extracardiac effects, some of which are adverse. The high prevalence of adverse effects has resulted in decreased use of the drug. The pulmonary, ophthalmologic, dermatologic, gastrointestinal, neurologic and thyroid systems may all be affected.[7]

The effects of amiodarone on thyroid function can be separated into two categories, iodine-induced effects and intrinsic drug effects. Outcomes can be further separated into two classes: disruption of thyroid hormone synthesis

Key points

- Amiodarone, an iodine-rich benzofuran derivative, is approved for the treatment of ventricular arrhythmias, but is often used in the treatment of atrial fibrillation
- Amiodarone and its active metabolite desethylamiodarone have multiple electrophysiologic effects
- Untoward effects associated with amiodarone use, including effects on the pulmonary, gastrointestinal, ophthalmologic, neurologic, dermatologic and thyroid systems, are prevalent and have resulted in decreased use of the drug
- Amiodarone-induced thyroid dysfunction, including hypothyroidism and hyperthyroidism, may be due to iodine effects or to intrinsic drug effects
- Treatment of amiodarone-induced thyrotoxicosis (AIT) varies depending on the type of AIT and does not necessarily include discontinuation of amiodarone treatment
- Dronedarone, a benzofuran derivative that does not contain iodine, has been approved by the FDA for the treatment of atrial fibrillation and demonstrates less thyroid-related toxic effects than amiodarone
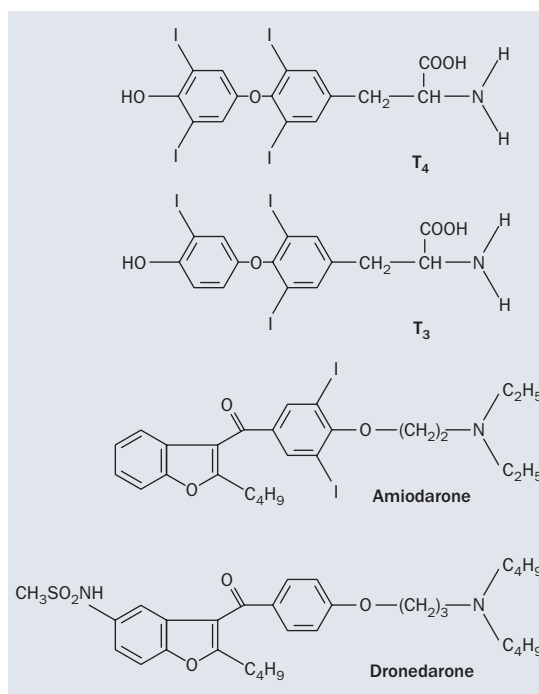

Figure 1 | Structures of T_3, T_4, amiodarone and dronedarone.

and direct damage to thyroid cells. Predisposing factors for amiodarone-induced thyroid dysfunction include environmental factors such as dietary iodine (deficiency), as well as intrinsic factors such as underlying thyroid status.

Thyroid hormone synthesis

The follicular cells of the thyroid gland, upon stimulation by TSH, synthesize thyroglobulin, the precursor of thyroid hormones (Figure 2). Thyroglobulin is then released into the space inside the follicle, which is filled with colloid. Iodide is trapped by the thyroid follicular cells, where it is oxidized by thyroid peroxidase into iodine and released into the colloid. Iodine is then incorporated into tyrosine residues within the thyroglobulin molecule, which then bonds with di-iodotyrosine and
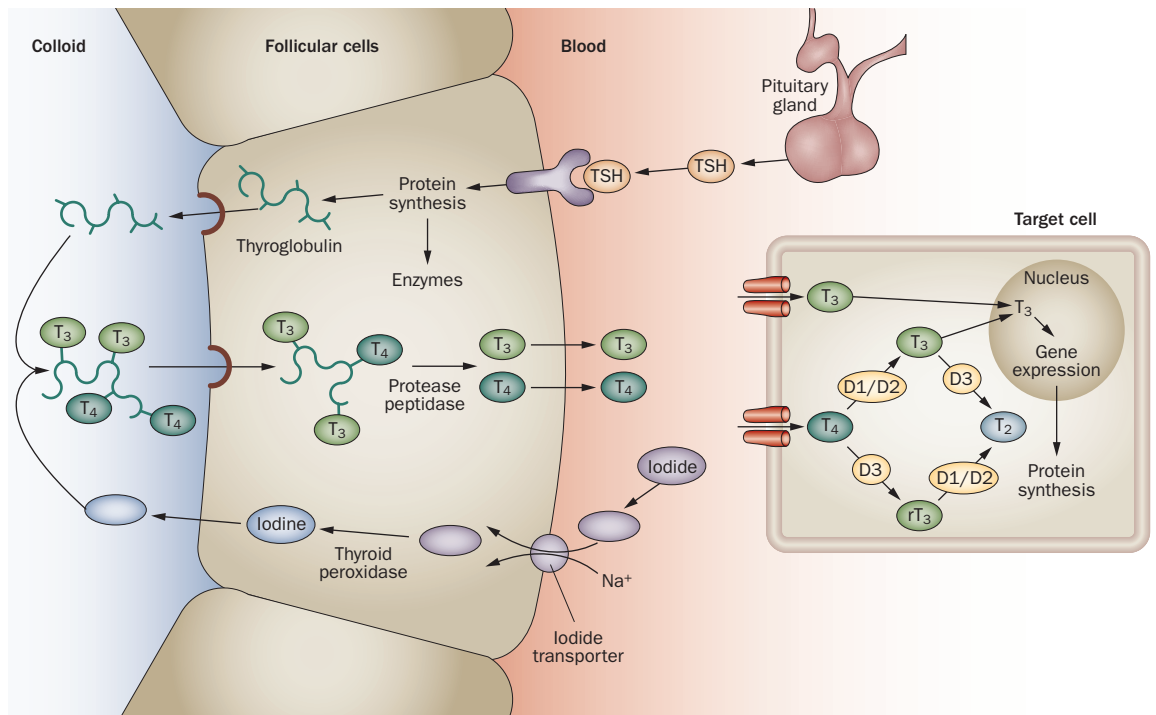
Figure 2 | Synthesis of thyroid hormones. Thyroid hormones are synthesized in follicular cells of the thyroid gland from tyrosine residues within the thyroglobulin molecule. T_4 and T_3 molecules are then cleaved and released into the circulation. T_3, the physiologically active form of thyroid hormone, can also be formed from the monodeiodination of T_4. T_4 is converted to T_3 predominantly by type I iodothyronine deiodinase. Abbreviations: D1, type I iodothyronine deiodinase; D2, type II iodothyronine deiodinase; D3, type III iodothyronine deiodinase; rT_3, reverse T_3.

monoiodotyrosine molecules; the combination of two di-iodotyrosine molecules forms T_4, while the combination of monoiodotyrosine with di-iodotyrosine forms T_3 (Figure 1). Following stimulation by TSH the thyroglobulin is reabsorbed into the follicular cells and the T_4 and T_3 molecules are cleaved and released into the circulation.[11,12]

T_3 can also be formed from the monodeiodination of T_4. This reaction, which is catalyzed by type I iodothyronine deiodinase (D1), is the predominant source of circulating T_3.[12] D1 is found largely in the kidney, liver and thyroid, while type II iodothyronine deiodinase (D2) is present primarily in skeletal muscle, the central nervous system and the pituitary. Type III iodothyronine deiodinase (D3), found in the brain, skin and placenta, inactivates T_4 and T_3 by inner-ring deiodination, which leads to the formation of reverse T_3 and T_2, respectively.[12]

Iodine-induced effects
Disruption to thyroid hormone synthesis and autoregulation owing to excess of iodine concentrations from amiodarone use may lead to either hypothyroidism or hyperthyroidism (thyrotoxicosis). Amiodarone-induced hypothyroidism (AIH) is due to the inhibition of iodide oxidation because of excess intrathyroidal iodine, which is known as the Wolff–Chaikoff effect. In individuals not receiving amiodarone, active transport of iodine into the thyroid follicular cells would be restored by autoregulation, despite high concentrations of iodine in

plasma, limiting inhibition to approximately 2 days.[13,14] Patients with underlying thyroid disease (autoimmune or goitrous) have an increased prevalence of failure to escape from the Wolff–Chaikoff effect, which results in sustained increase of TSH levels and can lead to thyroid-gland enlargement.

Amiodarone-induced thyrotoxicosis (AIT) also arises due to a failure of thyroid autoregulatory mechanisms that is thought to lead to thyroid autonomy, which is known as the Jod–Basedow effect.[15] This effect occurs typically in areas of iodine deficiency and in patients with underlying nodular or autoimmune thyroid disorders.

Intrinsic drug effects
In addition to iodine-related effects, amiodarone can alter the activity of deiodinase enzymes. The inhibition of D1 activity in peripheral tissues results in decreased T_3 concentration, increased total T_4 concentration and increased reverse T_3 concentration in serum (Figure 2).[7] While amiodarone inhibits D1 activity *in vivo*, this effect has not been demonstrated *in vitro*, whereas inhibition by this drug's metabolites has. This finding suggests that the effects observed *in vivo* may be caused by amiodarone metabolites competing with the D1 substrate T_4.[16] In addition to inhibition of D1 and pituitary D2 activity, decreased intracellular T_4 transport and decreased T_3 receptor binding in the pituitary gland lead to an initial increase in TSH concentration, but it gradually returns to baseline within 2–3 months.[6,17,18] These variations illustrate the 'amiodarone effect' on serum thyroid

function studies frequently observed in euthyroid subjects after initiation of treatment with amiodarone even in the absence of prior evidence of thyroid gland dysfunction.[15] With long term amiodarone treatment (>3 months) TSH levels will normalize, while total and free T_4 and reverse T_3 may be slightly elevated.[3] Because amiodarone has no effect on thyroxine-binding globulin concentrations, the fraction of free T_4 in total T_4 remains normal.[17]

Amiodarone-induced hypercholesterolemia, a hypothyroid-like condition in the liver, may be due to decreased expression of the LDL receptor gene, which is regulated by T_3.[2,18] Amiodarone and DEA also have a direct, dose-dependent cytotoxic effect on thyroid follicular cells.[2,7,19] The existence of a causal relationship between amiodarone and thyroid autoimmunity is controversial.[7]

Amiodarone-related adverse effects

Amiodarone-induced hypothyroidism

Epidemiology
Most patients treated with amiodarone will remain euthyroid throughout the treatment course.[3,20] As many as 10–20% of patients treated short term will manifest AIH.[3] AIH is more frequent in iodine-sufficient areas, with the incidence ratio for women and men being 1.5:1.[2,7,21,22]

Some studies suggest that the incidence of AIH decreases to 5–10% after long-term treatment (≥1 year) with amiodarone.[2,21,23] This reduction in prevalence may reflect adaptation of the thyroid autoregulatory mechanisms to iodine excess.[14] Alternatively, discontinuation of drug use (usually decided for reasons other than thyroid function) in patients where thyroid dysfunction has been detected would also result in a decreased prevalence. The presence of thyroid autoantibodies seems to increase the likelihood of developing AIH.[21,23] The risk of developing the disease is 14 times higher when a combination of pre-existing thyroid autoantibodies and female gender is present than in men without thyroid autoantibodies.[29]

Pathogenesis
Metabolic defects in thyroid hormone synthesis may be present in patients with a thyroid gland damaged by pre-existing Hashimoto thyroiditis and may in turn be responsible for the development of AIH. This group of patients is at the greatest risk of developing overt hypothyroidism. Alternatively, amiodarone may hasten the natural course of Hashimoto thyroiditis via iodine-induced damage to thyroid cells.[23] Other patients at risk are those that fail to escape from the Wolff–Chaikoff effect and develop permanent hypothyroidism.[24]

Clinical manifestations
The clinical manifestations of AIH are similar to those of primary hypothyroidism, including xerosis, fatigue, mental sluggishness and intolerance of cold. AIH may worsen ventricular irritability, for example torsades de pointes (a type of ventricular tachycardia), if hypothyroidism is sustained or severe. Less commonly, AIH has been associated with acute renal failure, which is reversible after treatment with levothyroxine and discontinuation of amiodarone.[26]

Diagnosis and treatment
The diagnosis of AIH is based on laboratory findings of decreased serum T_4 and increased serum TSH concentrations.[27] As recommended for mild or subclinical hypothyroidism, patients with serum TSH levels >10 mIU/l (even in the absence of symptoms) should be considered candidates for thyroid-hormone replacement therapy (Figure 3).[28] The treatment of choice for AIH is levothyroxine. Amiodarone can be continued at the discretion of the cardiologist, keeping in mind that spontaneous remission of hypothyroidism may occur. If amiodarone treatment is discontinued,[7] the decision to initiate thyroid hormone replacement can be delayed; if thyroid hormone treatment has been started, the dose of levothyroxine can be adjusted accordingly.[27,29] In such patients treated with levothyroxine, the goal of therapy is to ensure thyroid function does not worsen or, preferably, to achieve a euthyroid state. Thyroid function should be measured regularly throughout the duration of therapy to monitor treatment response. Treatment with levothyroxine has no effect on the antiarrhythmic properties of amiodarone.[30]

Amiodarone-induced thyrotoxicosis

Epidemiology
AIT has frequently been described in geographic areas with iodine deficiency.[22,31] The incidence of AIT reported in different studies varies but remains within the range of 5–10% in most studies.[32] The male-to-female incidence ratio is 3:1.[33] The time of onset of AIT is less predictable than that of AIH. It can occur at almost any time throughout the course of amiodarone treatment[21] and last for as long as 6–9 months after discontinuation of treatment, almost certainly because of the drug's long half-life and associated iodine load.

Pathogenesis
AIT can present in two forms, type 1 or type 2. Type 1 AIT results from the Jod–Basedow effect and is typically seen in patients with underlying thyroid dysfunction.[31,34] Type 2 AIT is caused by a destructive inflammatory thyroiditis with leakage of preformed hormone into the circulation following follicular cell damage.[7] Mixed forms of AIT often exist, and differentiating the two can be challenging.

Clinical manifestations
The reappearance or exacerbation of the underlying cardiac disorder after amiodarone is started, in a patient previously stable for their cardiac condition, should prompt an investigation into thyroid function.[7] Key symptoms of concern are an increase in the frequency and severity of ventricular arrhythmias or the new occurrence or increase in firing of an implantable cardiac defibrillator. Many patients with atrial fibrillation are treated with warfarin to lower the risk of clinical thromboembolism. Warfarin exerts its anticoagulation effect by inhibiting vitamin-K-dependent clotting factors II, VII, IX and X.[49] Although the pharmacokinetics of warfarin are unchanged in thyrotoxicosis, the rate of degradation of the coagulation factors dependent on vitamin K is
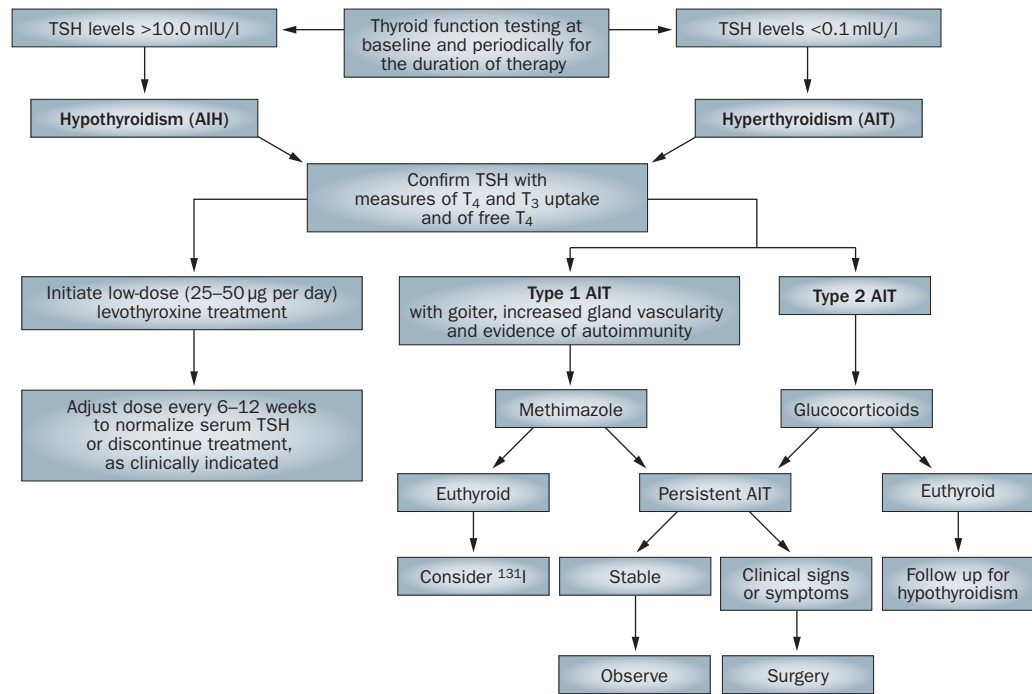
Figure 3 | Algorithm for management of amiodarone-induced thyroid disease. Amiodarone-induced thyroid disease can be diagnosed based on classic signs and symptoms of either hypothyroidism or hyperthyroidism or, more commonly, by routine (every 3–6 months) thyroid function testing. Any single abnormal TSH concentration (>10 mIU/l), an indication of clinical hypothyroidism (AIH), should be confirmed and treated with levothyroxine. AIT management depends upon the severity and duration of clinical signs or symptoms. Mixed type 1 and type 2 AIT may require combination therapy with thionamides and corticoid steroids. Abbreviations: AIH, amiodarone-induced hypothyroidism; AIT, amiodarone-induced thyrotoxicosis.

increased in this setting, which results in potentiation of warfarin effects.[35] Therefore, an unexplained change in warfarin sensitivity requiring a decrease in dosage should lead the treating physician to suspect hyperthyroidism. Other clinical conditions associated with both types of AIT are goiter and orbitopathy, although these conditions are not always present unless the patient has underlying Graves disease.[7]

Diagnosis

The diagnosis of AIT is most commonly made when TSH levels are found to be decreased and total serum T_3 levels increased in the course of routine thyroid function tests. Serum concentrations of T_4 may be a less useful indicator of hyperthyroidism than those of T_3 because decreased conversion of T_4 to T_3 often takes place after the initiation of amiodarone treatment without hyperthyroidism being present.[2,36]

The existence of thyroid abnormalities, such as diffuse or multinodular goiter and Graves disease, which may give rise to functional autonomy in the setting of iodine excess, may be an indication of type 1 AIT. Increased concentrations of thyroid autoantibodies, such as anti-thyroglobulin, antithyroid peroxidase and TSH-receptor antibodies, as well as T-cell populations specific for Graves disease, have been demonstrated in patients with type 1 AIT.[6,21,23]

Type 2 AIT is primarily a thyroid inflammatory process and occurs in patients with otherwise clinically normal thyroid glands at presentation. Histopathological effects of amiodarone include follicular damage, disruption by fibrosis, epithelial atrophy, and lymphocyte infiltration.[19,37] The levels of interleukin 6 (IL-6), a cytokine that is a general marker of thyroid inflammatory processes,[37] are slightly elevated in type 1 AIT but markedly elevated in type 2 AIT.[7] The specificity of IL-6 measurements to distinguish type 1 from type 2 AIT, however, has been called into question, as different studies had distinct results.[38,39] Color flow Doppler ultrasonography is a procedure that shows intrathyroidal blood flow.[40] Patients with type 1 AIT typically show normal or increased vascularity similar to spontaneous hyperthyroidism, whereas those with type 2 AIT show absent vascularity.[40]

24 h radioactive iodine uptake is usually undetectable or low in patients with iodine-induced AIT.[41] In patients with type 1 AIT living in iodine-deficient areas, radioactive iodine uptake may be higher than 10% despite iodine excess.[7] This finding may arise because of the failure of the autoregulatory mechanism of the thyroid gland to decrease iodine trapping, which results in increased intrathyroidal iodine stores.[41] By contrast, patients with type 2 AIT will typically have a radioactive iodine uptake of <1% because their thyroid glands are partially destroyed by the underlying disease.[7] In practice, however, radioactive iodine uptake measurement is often not helpful to differentiate type 1 from type 2 AIT.

Management and treatment

AIT may resolve spontaneously in approximately 20% of patients, most of whom with type 2 AIT.[38] Patients

who develop both types of AIT have an increased risk of major adverse cardiovascular events, including myocardial infarction, stroke and ventricular arrhythmias, compared with euthyroid amiodarone-treated individuals.[42] This observation strongly implies, but does not prove, that careful surveillance and prompt effective treatment are needed in patients receiving amiodarone when high-risk factors for AIT are present.[42] Therefore, all patients for whom amiodarone treatment is planned should undergo baseline thyroid function studies, including TSH, T_4 and T_3 uptake tests, and periodically thereafter. This screening is important because the traditional symptoms of hyperthyroidism may by absent in patients who develop AIT, owing to the decreased conversion of T_4 to T_3 and the antiadrenergic effects of amiodarone.[7] In the presence of a history of thyroid disease, strong family history of thyroid disease or palpable thyroid gland abnormalities, additional testing such as measurement of antithyroid antibodies or thyroid ultrasonography may be considered.[21,23]

The management of AIT can be quite challenging. In the USA, most cases of AIT are type 2, and it is often difficult to identify cases of 'pure' type 1 disease. Patients with type 1 AIT should be treated with thionamides (methimazole 40–60 mg per day) to block thyroid-hormone synthesis (Figure 3). In the setting of iodine excess increased dosages of thionamides may be required, as patients develop drug resistance.[43,44,45] Definitive treatment of type 1 AIT may be accomplished with surgery or radioactive iodine treatment if radioactive iodine uptake values are sufficiently high (>10%) after the patient becomes euthyroid.[7] Type 2 AIT is responsive to glucocorticoid therapy at doses of 30–40 mg per day for a duration of 1–3 months.[7,43,44] For patients with mixed forms of AIT, therapy directed at both subtypes should begin with glucocorticoids and thionamides,[6] although some studies have indicated that the latter might not be very useful.[7,17,46,47] If medical therapy is unsuccessful, surgical treatment of AIT will result in prompt control of thyrotoxicosis, and is especially useful if cardiovascular complications require rapid intervention.[7,17,43,44,48] In the past, physicians and surgeons have been adverse to surgical thyroidectomy as a treatment option because of the increased risks of associated anesthesia and surgery in this group of patients.[48] However, multiple studies have reported favorable outcomes of thyroidectomy and, when balanced against long-term uncontrolled AIT, the risk-to-benefit ratio can be viewed as desirable.[48,49]

Potassium perchlorate blocks thyroid-hormone production by competitively interfering with iodide trapping, and causes release of iodide from thyroid glands in which the iodide oxidation process is defective.[50] Perchlorate has been used for the treatment of type 1 AIT, although not all treated patients improve.[50] Unfortunately, long-term use of perchlorate is limited by its toxic effects; specifically, it may cause agranulocytosis and aplastic anemia.[7,50,51] In addition, perchlorate is not available in all areas, such as in the USA.

The biological effects of amiodarone persist long after cessation of treatment. Remarkably, amiodarone may protect the heart from the localized effects of thyrotoxicosis due to its intrinsic inhibition of β-adrenergic receptors and related decreased conversion of T_4 to T_3. Thus, discontinuation of the drug may actually worsen thyrotoxic effects on the heart.[17,43,45] In light of these considerations, the decision to stop treatment with amiodarone will depend on the underlying cardiac problem for which treatment was started, and the extent to which the patient is likely to respond or responds to other medical therapies.[17,27,29,52,53]

Dronedarone

Dronedarone was approved by the FDA in July of 2009 for the treatment of atrial fibrillation. Dronedarone is, like amiodarone, a benzofuran derivative and was developed with the goal of replicating the antiarrhythmic effects of amiodarone while limiting the associated toxic effects. Dronedarone is structurally related to amiodarone but does not contain iodine atoms (Figure 1). Dronedarone has a very short half-life compared with amiodarone (30 h versus 40 days) and is less lipophilic because of its additional methane-sulfonamyl group.[20,54] The bioavailability of dronedarone is 15% owing to substantial first-pass metabolism, and peak plasma concentrations of dronedarone are achieved within 3–6 h.[20] At an average dose of 400 mg twice daily, steady state is reached within 4–8 days of treatment. The metabolites of dronedarone are excreted primarily in the feces, with renal excretion playing a minor role in elimination (6%).[20] Dronedarone demonstrates similar electrophysiologic properties to those of amiodarone.[54]

Safety and efficacy

To assess the safety and efficacy of dronedarone, six multicenter studies were conducted. In these studies, over 3,000 patients were treated with dronedarone at doses of 400 mg twice daily for an average of 12 months. The EURIDIS and ADONIS trials were identical, multicenter, double-blind, randomized trials with the goals of assessing the 1-year efficacy of dronedarone to maintain sinus rhythm after electrical, pharmacological, or spontaneous conversion of atrial fibrillation or atrial flutter, compared with placebo.[55] These trials demonstrated that 1 year of treatment with dronedarone significantly decreased the risk of first recurrence of atrial fibrillation or atrial flutter, reduced the time of first recurrence of either state, slowed ventricular response in patients whose atrial fibrillation or atrial flutter recurred, and was associated with lower risk of hospitalization for cardiovascular events.[20,55] The ERATO trial[56] was a multicenter, double-blind, randomized trial comparing the efficacy of taking 400 mg dronedarone twice daily with that of placebo in controlling the ventricular rate in patients with symptomatic atrial fibrillation.[20,56] The authors concluded that dronedarone reduces the ventricular rate of patients with permanent atrial fibrillation.[56]

ANDROMEDA,[57] the first outcome trial of dronedarone, was a randomized double-blind, placebo-controlled trial that evaluated the risk of hospitalization for worsening heart failure or death in patients hospitalized for decompensated heart failure.[20,56–58] This study was

terminated prematurely when taking dronedarone was associated with increased risk of death.[57] ATHENA[59] was developed to focus on the excess morbidity and mortality reported in ANDROMEDA. It was a randomized, double-blind, placebo-controlled trial to evaluate the long-term effect of dronedarone versus placebo on the combined risk of cardiovascular hospitalizations and all-cause mortality in patients with recent or current history of atrial fibrillation and/or flutter.[20,55,59] In marked contrast to ANDROMEDA, ATHENA reported a 24% reduction in the combined end point in the dronedarone group compared with the placebo group. The discrepancy between the results of the ANDROMEDA and the ATHENA studies has been attributed to differences in patient stability, to use of inhibitors of angiotensin-converting enzyme and of angiotensin receptor blockers in the ANDROMEDA trial and to the reliability of the findings.[20]

Toxic effects

The major adverse effects associated with dronedarone are gastrointestinal (diarrhea, nausea and/or vomiting), elevated serum creatinine concentrations (caused by inhibition of creatinine excretion at the tubular level, with no change in glomerular filtration rate),[60] rash and cardiac effects known to be associated with this class of antiarrhythmic (bradycardia and QT interval prolongation).[20,54,55] The incidence of serious adverse events is similar to that among patients receiving placebo.[20]

In the EURIDIS and ADONIS trials, the incidence of clinical hyperthyroidism was 8.4% in the dronedarone group versus 14.1% in the placebo group ($P = 0.002$) and the incidence of hypothyroidism was 5.5% in the dronedarone group versus 3.5% in the placebo group ($P = 0.15$).[54] One of the causes of atrial fibrillation, a study entry criteria, is thyrotoxicosis, which may explain the high incidence of hyperthyroidism in the placebo group. The incidence of hyperthyroidism or hypothyroidism did not differ significantly between the placebo and dronedarone groups in the ATHENA trial, for unknown reasons.[54] These studies suggest that, in marked contrast to the experience with amiodarone, there is no increase in clinical thyroid disease in patients treated with dronedarone.

The DIONYSOS study[20] was a double-blind trial designed to compare the ability of dronedarone and amiodarone to maintain sinus rhythm in 504 patients (249 and 255 patients, respectively) with atrial fibrillation, followed up for at least 6 months. In contrast to prior studies, all patients had serial measures of thyroid function. At baseline, 5% of patients in both the amiodarone and the dronedarone groups had hypothyroidism and <1% of patients had hyperthyroidism. The study showed that 79% of patients treated with dronedarone and 50% of those treated with amiodarone had normal thyroid function at baseline, which was maintained during treatment. Overall, 105 (41%) amiodarone-treated patients, euthyroid at baseline, demonstrated changes in thyroid function consistent with an alteration in thyroid hormone metabolism and the development of hypothyroidism, compared with 30 patients (12%) treated with dronedarone and also euthyroid at baseline ($P < 0.001$). For the most severe amiodarone-related adverse effect, AIT, the incidence was 6% in the amiodarone group and 1% in the dronedarone group, in previously euthyroid patients.

Conclusions

Amiodarone is a highly effective medication used for the treatment of many cardiac arrhythmias. The consequences of amiodarone use include adverse effects that may be unacceptable to patients and treating physicians. Thyroid dysfunction may occur following amiodarone therapy, ranging from derangements in thyroid function in euthyroid patients to overt hypothyroidism or hyperthyroidism, the latter of which can be extremely challenging to diagnose and even more so to treat. Dronedarone may be beneficial to treat patients with atrial fibrillation or flutter, who are at risk of developing amiodarone-induced thyroid dysfunction.

Review criteria

A search of PubMed was performed and updated through September 2009. The search included the following search terms, individually and in combination: "amiodarone", "thyroid", "hypothyroidism", "hyperthyroidism", "dronedarone", "toxicity", "thyrotoxicosis", "atrial fibrillation", "arrhythmia", "desethylamiodarone", "ventricular arrhythmia", "ERATO study", "amiodarone induced thyroid dysfunction", "pharmacokinetics", "wolff-chaikoff effect", and "review". Literature review included the years from 1963 to present. All papers were in English. Full papers were acquired and relevant references from these publications were also retrieved.

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