Amiodarone and the Thyroid

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An antiarrhythmic drug, amiodarone, contains 37% iodine by weight and is structurally similar to the thyroid hormones. The drug inhibits hepatic 5'α-deiodinase, resulting in increases in serum thyroxin and “reverse” triiodothyronine, whereas the concentration of triiodothyronine in serum is decreased. There is a significant incidence of either hypothyroidism or hyperthyroidism in patients who are being treated with the drug. This is largely the effect of iodine released from the drug during chronic therapy, but in susceptible individuals amiodarone may unmask autoimmune thyroid disease. Some effects of the drug suggest that it may interfere with the action of thyroid hormones at the cellular level, inducing a state of localized hypothyroidism.

Amiodarone is a drug with unique pharmacological and electrophysiological properties. It has complex effects on peripheral iodotyroxine metabolism and, because of iodine released during chronic therapy, it also may affect the function of the thyroid gland directly. The drug is effective in a wide range of cardiac rhythm disturbances, including those refractory to the traditional agents, and it exerts a significant anti-arrhythmic action, lacking the hemodynamic disadvantages of other antiarrhythmic drugs. The use of amiodarone is increasing, especially in nonspecialist centers. The mechanism of the interaction of the drug with the thyroid is not widely understood, but changes in practice mandate that both clinician and clinical biochemist be able to assess thyroid status in patients taking amiodarone.

Pharmacology

Amiodarone is a benzofuran derivative containing a phenol moiety with two atoms of covalently bound iodine (Figure 1). It selectively prolongs the duration of the cardiac action potential, and thus the effective refractory period of conducting tissue. In the classification of antiarrhythmic drugs devised by Vaughan Williams (1), the drug is therefore a class III agent. Recently, amiodarone has also been reported to decrease automaticity and conduction in cardiac tissue. Highly lipophilic, the drug rapidly becomes widely distributed in tissues, including cardiac muscle. It is also very highly bound to plasma protein and highly metabolized, with little of the drug appearing unchanged in the urine (2–4).

Steady-state concentrations in the plasma are only slowly achieved after oral administration of the drug. Little information is yet available concerning the amount of iodine released during chronic treatment with amiodarone. A value of 6 mg of iodine per day for each 200-mg tablet has been suggested (5). With the usual maintenance dose of amiodarone being between 200 and 600 mg per day, as much as 18 mg of iodine per day may be released from the drug. This is considerably in excess of the average daily intake of dietary iodine, which seldom exceeds 700 µg and is usually <200 µg per day (6). Amiodarone therapy thus presents a considerable iodine load to the thyroid.

Elimination of the drug is biphasic, with an initial rapid phase followed by a prolonged period of slow elimination; significant concentrations of the drug remain detectable many weeks after cessation of therapy (7).

Although generally well tolerated, the drug has been associated with a wide spectrum of side effects: dermatological, ocular, neuromuscular, hepatic, and pulmonary. A photosensitive skin rash is the most common troublesome adverse effect of the drug, whereas corneal microdeposits of the drug, although they occur in most patients, do not usually give rise to symptoms. Neuromuscular reactions are usually mild, but symptomatic peripheral neuropathy may occur. Changes in hepatic enzymes occur in up to 20% of patients, although frank liver disease is a relatively rare complication of therapy with amiodarone. Pulmonary fibrosis, a severe and life-threatening complication, fortunately is extremely rare (8). The drug almost invariably affects results of thyroid-function tests and is associated with an appreciable incidence of frank thyroid dysfunction. Abnormalities of thyroid function may occur for the first time or continue after amiodarone treatment has been stopped, owing to the extremely slow elimination of the drug.

Thyroid-Function Tests

Biochemical changes during therapy with amiodarone are common (Table 1) but usually not clinically significant. Increases in plasma thyroxin (T₄) with the drug have been long recognized and confirmed in a number of studies (9–13). This increase in T₄ parallels the decrease in heart rate induced by the drug (14). Neither the concentrations of thyroid-hormone-binding proteins nor the binding of iodo-
thyroxines to these proteins is changed. Thus both total and free T₄ are increased. In the early days of therapy, T₄ production by the gland may decrease and T₄ concentrations decline (10), probably owing to the acute inhibitory effect of the excess iodine on the release of hormone from the thyroid. Known as the Wolff–Chaikoff effect (15), this is generally short-lived. The acute inhibitory effect of iodine excess has been reported in normal human subjects by Vegenakis et al. (16), who demonstrated decreased thyroid hormone concentrations in serum of volunteers given potassium iodide. Decreases in total and free triiodothyronine (T₃) concentrations in plasma are usually modest and values are frequently within the normal reference interval (9, 10, 12). The concentration of plasma "reverse" T₃ is consistently increased during amiodarone therapy (10, 12, 13). These changes in thyroid hormones may take some weeks to develop, but tend to persist throughout treatment with the drug. Plasma rT₃ concentrations may relate to the clinical effects of amiodarone, with satisfactory thyroid control usually apparent at 500–1000 ng/L (normal <500 ng/L), whereas adverse effects are associated with rT₃ concentrations >1000 ng/L (17). Thus, measurement of rT₃ may be a convenient alternative to monitoring concentrations of the drug itself. The pattern of changes in iodothyrines with amiodarone is attributable to inhibition of hepatic 5′-deiodinase and resembles that after use of roentgenographic contrast media such as iopanoic acid, which also produce a transient increase in TSH (18). The increase in TSH with amiodarone treatment (10, 13, 19) usually occurs only during the first few weeks of treatment. Concomitantly, the response of TSH to thyrotropin may be exaggerated. It is not clear whether this change in TSH secretion results from the lower T₄ concentration present or from a direct action of the drug on the thyrotrhop cells of the pituitary. In the longer term, TSH concentrations are usually within the normal range in euthyroid subjects, but decreased TSH with diminished thyrotrpin response has been noted in patients with treated hypothyroidism who are taking amiodarone (20).

Iodothyronine Kinetics

The concentration of a hormone in plasma represents a balance between rates of production and metabolic clearance. The effect of amiodarone on iodothyronine kinetics has been determined by use of isotopic techniques. Lambert et al. (21) have shown increased T₄ production and reduced clearance in patients during chronic oral therapy. By contrast, Hershman et al. (22) found no change in the T₄ clearance after six weeks of amiodarone therapy in patients with supraventricular arrhythmias.

T₃ production is inhibited by amiodarone, but clearance is not affected (21). The major source of T₃ is the liver, where it is produced by outer-ring deiodination of T₄ at the 5′ position by "type I" deiodinase. Inhibition of this enzyme by amiodarone has been demonstrated in rat-liver homogenates (23, 24) and also in isolated hepatocytes (25). Reduced conversion of T₄ to T₃ has been confirmed in human subjects who have been given radiolabeled T₄ (22). Amiodarone not only may inhibit T₃ production by reducing enzymatic conversion from T₄, but also may inhibit the uptake of iodothyronines by the liver (26). Kaptein et al. (27) used compartmental analysis to study T₄ kinetics, and demonstrated that amiodarone can reduce the fractional rate of T₄ transfer between serum and the rapidly equilibrating tissue pool. Because this effect is not caused by alterations of binding proteins, as already discussed, it may reflect inhibition of the T₄-transport mechanism.

There are no satisfactory human data for rT₃ kinetics and, currently, the only available information is from experiments in rabbits (28). The production of rT₃ by inner-ring deiodination of T₃ at the 5′ position occurs predominantly in extrahepatic tissues and is unaffected by amiodarone. Clearance of rT₃ is initially by 5′ deiodination in the liver and is inhibited by the drug.

Interaction with iodothyronines at the Cellular Level

The biologically most potent thyroid hormone is T₃, which is taken up into cells by a saturable, membrane-receptor mediated, energy-dependent mechanism. T₃ exerts its action on the cell via a nuclear receptor, which is a nonhistone protein tightly bound to DNA. The receptor, the product of the c-erb-A oncogene, is part of a family of regulatory gene products, which includes the steroid hormone receptors (29). The action of thyroid hormones has been studied by using pituitary cells secreting growth hormone in culture. The binding of T₄ to its receptor is followed rapidly by increased formation of mRNA coding for growth hormone. The rate of transcription is proportional to the concentration of thyroid hormone receptor complexes (30). De Nayer (31) found that 85% of the iodothyronine bound to these receptors is T₃.

Amiodarone may have specific effects on different tissues at the cellular level, inducing localized states of apparent thyroid imbalance. In the pituitary, TSH secretion may be increased despite high circulating concentrations of T₄, suggesting a direct effect of the drug on thyrotrphs. These cells, like others in the central nervous system, convert T₄ to T₃ by a "type II" deiodinase, distinct from the enzyme in the liver. Thyrotrphs in vivo and in vitro respond to exogenous T₃, but locally produced T₃ may contribute substantially to the thyroid hormone status of these cells. Type II deiodinase has a lower Kₘ for T₄, and is not sensitive to propylthiouracil (32). It displays increased activity in patients with hypothyroidism, in contrast to the type I enzyme (33). Normally, TSH secretion is inhibited by T₃. Franklyn et al. (19) have shown that amiodarone inhibits T₃ binding to pituitary nuclei and directly promotes TSH secretion. They have further shown, in rats, that amiodarone enhances the production of messenger RNA coding for both alpha- and beta-subunits of TSH (34). Inhibition of nuclear T₃ binding cannot be a general property of the drug, because amiodarone has been shown not to affect binding to the nuclei of dispersed human fibroblasts (35). Studies of cell growth of cultured CHO pituitary cells have demonstrated that amiodarone also inhibits T₃-stimulated incorporation of [³H]thymidine into DNA (36). Pituitary TSH secretion may also be enhanced after inhibition of the type II deiodinase by the increased concentrations of

**Table 1. Changes in Thyroid-Function Test Results during Chronic Amiodarone Therapy**

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<thead>
<tr>
<th>Hormone measured</th>
<th>Change with amiodarone</th>
<th>References</th>
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<tbody>
<tr>
<td>Thyroxin, total and free</td>
<td>Increase</td>
<td>8–13</td>
</tr>
<tr>
<td>Triiodothyronine, total and free</td>
<td>Decrease</td>
<td>8, 9, 11</td>
</tr>
<tr>
<td>Reverse T₃</td>
<td>Increase</td>
<td>9, 11, 12</td>
</tr>
<tr>
<td>Thyrotropin</td>
<td>Increase (short term)</td>
<td>9, 12, 18</td>
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rT₃ prevailing in amiodarone-treated patients (37). Indeed, inhibition of type II deiodinase by amiodarone has been demonstrated in hypothyroid rats (38). Increased concentrations of rT₃ decrease the amount of T₃ available for feedback inhibition in the thyrotrhop. It is not clear at present why the increase in TSH during amiodarone therapy is usually limited to the first few weeks of treatment. This change is not always due to observed alterations in circulating thyroid hormone concentrations, but may be due to a state of apparent hyperthyroidism in the thyrotrhop induced by the drug.

Selective inhibition of thyroid hormone action on the myocardium could explain some of the cardiac effects of amiodarone. Many of the effects of amiodarone on the heart resemble those seen in hypothyroidism—bradycardia, reduced myocardial oxygen consumption, decrease in tension-time index, prolongation of action-potential duration (39), and changes in myosin ATPase (23). Singh and Vaughan Williams (40) found that, in rabbits, Lugol's iodine had no effect on action-potential duration, but the effects of amiodarone were antagonized by T₃ administration. Oral T₃ has not, however, been found to antagonize the antiarrrhythmic action of amiodarone in humans (41). Iopanoic acid produces changes in thyroid hormones similar to those of amiodarone but has no antiarrrhythmic action (42). Inhibition of deiodinase is not the only mechanism by which amiodarone may inhibit thyroid hormone action on the heart: its effect on iodothyronine uptake, nuclear binding, and binding to the recently described cytosolic T₃-binding proteins (43) is not known. Reduced nuclear binding of iodothyronine in cardiac muscle induced by amiodarone has been demonstrated in one study (44), but it is still not clear whether amiodarone may act by inducing a local state of hyperthyroidism in cardiac tissue.

Appreciable quantities of amiodarone accumulate in the thyroid (3). Gluzman et al. (45), in a study using pig thyroid slices in culture, found that the drug did not affect intrathyroidal iodine metabolism at the doses found in the serum of patients during amiodarone treatment. Recent observations on human thyroid, both in vivo (46, 47) and in vitro (48), suggest that amiodarone may exert a toxic effect on the gland. In vitro studies with amiodarone are hampered by the drug's insolubility in aqueous solution. The direct actions of amiodarone on the thyroid require further study.

Thyrotoxicosis

Sporadic cases of thyrotoxicosis with amiodarone have been well described but the condition has only recently been systematically studied. Estimates for the prevalence of hyperthyroidism in amiodarone-treated patients vary between 1% and 15% (49, 50). In most cases, the thyrotoxicosis appears to be iodine-induced. Unlike spontaneous thyrotoxicosis, the condition is slightly more common in males than in females (51). Iodine in excess usually inhibits the thyroid (52), but may occasionally precipitate thyrotoxicosis, particularly in patients with pre-existing thyroid abnormalities (53, 54) such as subclinical thyroid autonomy. In a proportion of patients with iodine-induced thyrotoxicosis, no pre-existing thyroid abnormality can be identified (55). Amiodarone therapy is now the most common cause of this clinical entity. Martino et al. (56) have compared the incidence of thyroid dysfunction in an area of low iodine intake (Tuscany, Italy) with that in an iodine-replete area (Massachusetts, USA). Thyrotoxicosis was more common in Tuscany (9.6%) than in Massachusetts (2%). The incidence of amiodarone-induced hyperthyroidism is generally low in areas of iodine repletion (57–59). The condition may occur after amiodarone therapy has been withdrawn (60).

Symptoms of hyperthyroidism may be masked by the patient's condition and by the effects of amiodarone. A small, often transient, goiter may be present (55, 61, 62), but dermopathy or ophthalmopathy of the sort found in Graves' disease is not a feature of amiodarone-induced hyperthyroidism. Thyroid-stimulating immunoglobulins, diagnostic of Graves' disease, are not usually detected (56, 63), suggesting that most cases are not autoimmune in origin. No single biochemical test will reliably predict thyroid dysfunction caused by amiodarone (64), and careful clinical evaluation is necessary in each case. Concentrations of total and free thyroid hormones are increased in most cases, but the total T₄ value may be within the normal range (55) and, as in iodine-induced thyrotoxicosis from other causes, the T₃ concentration may also be normal (46, 53). TSH is suppressed and does not respond to intravenous injection of thyrotilberin. Measurement of rT₃ does not help in the diagnosis or management of hyperthyroidism. Isotope tests are of no value, because uptake of iodine by the gland is suppressed (46, 65).

Treatment of amiodarone-induced thyrotoxicosis can be difficult. If possible, the drug should be withdrawn, at least temporarily. In deciding on therapy, one should bear in mind that this type of hyperthyroidism frequently remits spontaneously within six months (46, 65). Destructive antithyroid therapy is not, in any case, usually appropriate, because the underlying rhythm disturbance makes elective surgery undesirable, and suppression of iodide uptake by the gland precludes radio-ablation except with very high doses of radioactivity. Thionamide drugs are less effective than in patients with spontaneous hyperthyroidism. Propylthiouracil is to be preferred to carbimazole or methimazole because of its additional peripheral action in reducing T₄ production. Recently, the combination of thionamide with potassium perchlorate has been advocated (56) and may be of some benefit. Corticosteroids also reduce iodide utilization by the gland and have been shown to hasten euthyroidism in amiodarone-induced thyrotoxicosis (46, 61).

Hypothyroidism

The dominant effect of excess iodide on normal thyroid tissue is to inhibit the synthesis and release of hormone, both in vivo (52) and in vitro (66). Hypothyroidism is a well-described complication of amiodarone therapy (58, 67–71). It is often mild, but severe myxedema can result (72). In areas of iodine repletion, hypothyroidism is a more common complication than thyrotoxicosis (49, 56). For example, Martino et al. (56) found the incidence of hypothyroidism in Massachusetts to be 22%, compared with 5% in Tuscany. Hypothyroidism due to amiodarone is more common in females, many of whom have pre-existing thyroid abnormalities, such as thyroid autoantibodies (73). Most cases occur within the first year of amiodarone therapy (60), and about 50% have circulating antithyroid antibodies when hypothyroidism is diagnosed (56, 73). Some cases may, therefore, be due to autoimmune thyroiditis in susceptible subjects, whereas others result from the inhibitory effects of iodine on the gland. The latter group may include patients whose hypothyroidism is reversible if the use of the drug is discontinued (73, 74). The relative contribution
of autoimmunity and iodide inhibition is hard to assess and the presence of circulating autoantibodies to the thyroid is not necessarily diagnostic of an autoimmune disease. In the study by Foresti et al. (75), antithyroid antibodies were found not to predict the development of hypothyroidism with amiodarone. Patients with Hashimoto's thyroiditis are known to be more susceptible to the inhibitory effects of iodide on the gland (76). A phase of temporary hypothyroidism is common in patients recovering from iodine-induced thyrotoxicosis, including that caused by amiodarone (46, 55), and permanent hypothyroidism has also been reported (77).

There are no clinical features peculiar to amiodarone-induced hypothyroidism. The concentrations of thyroid hormones in serum are usually decreased, although the total T4 concentration may be within the reference range. An increase of TSH concentration after the first few weeks of therapy is strongly suggestive of developing hypothyroidism. The anticipated increase in rT3 concentration may not occur in hypothyroid patients. Treatment is with T3 in the usual doses and as guided by the clinical state. Amiodarone and T4 may be used concurrently.

Amiodarone and Thyroid Autoimmunity

There is controversy concerning the relationship between amiodarone and autoimmune phenomena. Rabinow et al. (78) reported a high frequency of thyroid autoantibodies and alterations in a regulatory subset of T-lymphocytes in euthyroid patients taking amiodarone. This may be due to iodine excess, which can modulate the development of thyroid autoimmunity (79). Boukis et al. (80) have shown that treatment of iodine-deficient subjects with iodized oil results in the development of autoantibodies in many cases. Iodine stimulates the synthesis of immunoglobulin G by peripheral blood lymphocytes in vitro (81).

Amiodarone can clearly unmask autoimmune thyroid disease, particularly that leading to hypothyroidism, in susceptible individuals. Caution should therefore be exercised in prescribing the drug to patients with a personal or family history of thyroid disease or those with circulating antibodies to the thyroid. Autoantibodies are not usually found in patients developing hyperthyroidism with amiodarone, although Omri-Delangen et al. (82) have described stimulation of thyroid adenylate cyclase by immunoglobulins purified from patients taking amiodarone. Monteiro et al. (83), in a study conducted in an iodine-deficient area of Portugal, found autoantibodies in half of their euthyroid patients after amiodarone treatment; however, their findings are not in agreement with two further recent studies (66, 64) in which the incidence of autoantibodies was low. Thyroid autoimmunity may be more common in patients with ischemic heart disease (85), which must be taken into account when assessing studies such as those quoted. Although some patients with amiodarone-induced hypothyroidism may have autoimmune thyroiditis, most cases of thyroid dysfunction with amiodarone do not appear to be of autoimmune origin.

Conclusion

Changes in thyroid-function tests are almost invariably found in patients taking amiodarone: total and free T4 and rT3 concentrations are increased, and T3 is modestly decreased; TSH may be increased in the early weeks of therapy. These changes are usually due to the drug's extra-thyroidal actions and do not indicate thyroid dysfunc-

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