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Chapter 4

Amiodarone and thyroid

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ABSTRACT

Assessment of TSH and TPO-Ab before starting amiodarone (AM) treatment is recommended. The usefulness of periodic TSH measurement every 6 months during AM treatment is limited by the often sudden explosive onset of AIT, and the spontaneous return of a suppressed TSH to normal values in half of the cases. AM-induced hypothyroidism develops rather early after starting treatment, preferentially in iodine-sufficient areas and in females with TPO-Ab; it is due to failure to escape from the Wolff–Chaikoff effect, resulting in preserved radioiodine uptake. AM-induced thyrotoxicosis (AIT) occurs at any time during treatment, preferentially in iodine-deficient regions and in males. AIT can be classified in type 1 (iodide-induced thyrotoxicosis, best treated by potassium perchlorate in combination with thionamides and discontinuation of AM) and type 2 (destructive thyrotoxicosis, best treated by prednisone; discontinuation of AM may not be necessary). AIT is associated with a higher rate of major adverse cardiovascular events (especially of ventricular arrhythmias). Uncertainty continues to exist with respect to the feasibility of continuation of AM despite AIT, the appropriate methods to distinguish between AIT type 1 and 2 as well as the advantages of AIT classification into subtypes in view of possible mixed cases, and the best policy when AM needs to be restarted.
Pharmacology of amiodarone

Amiodarone (AM), introduced as an anti-anginal compound in 1962, has emerged as a uniquely effective anti-arrhythmic drug with a multiplicity of properties. Most striking is the lengthening of the repolarisation in the atria and ventricles associated with bradycardia but without a significant propensity for inducing torsades de pointes. AM is now the most frequently used drug for maintaining sinus rhythm in patients with atrial fibrillation. The drug has, however, many, sometimes severe, side effects.

AM is an amphiphilic drug with hydrophilic (tertiary amine) and lipophilic (benzofuran and diiodinated benzene ring) moieties, with a structural resemblance to thyroid hormones (Fig. 1). Desethylamiodarone (DEA) is the main metabolite of AM, containing all properties of its parent drug. AM is prescribed as amiodarone hydrochloride (MW 681.82), containing 37.25% iodine by weight. Pharmacokinetic studies in humans indicate a very long elimination half-life (40 ± 10 days and 57 ± 27 days for AM and DEA, respectively), a large distribution volume (106 ± 38 l kg⁻¹) and extensive tissue distribution. Highest levels are found in adipose tissue (316 and 76 μg g⁻¹ of AM and DEA, respectively), liver (391 and 2354 μg g⁻¹, respectively) and lung (198 and 952 μg g⁻¹, respectively), but thyroidal concentrations are still substantial (14 and 64 μg g⁻¹ of AM and DEA, respectively) (data from human autopsies). The slow turnover of the drug from the stock or ‘deep’ compartment explains the exceptionally long terminal half-life. AM as an amphiphilic drug accumulates in lysosomes, binding to intralysosomal phospholipids; the bound complexes, indigestible by phospholipases, form the intralysosomal multilamellar inclusion bodies observed in many organs (such as lung, liver, heart, skin, corneal epithelium and peripheral nerve fibres). The findings suggest a drug-induced phospholipidosis with disturbances of lysosomal function as an explanation of the side effects of AM. The mechanism of AM toxicity is, however, likely multifactorial; accumulation of iodine, the formation of free radicals and immunologic injury are also involved.

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AM undergoes extensive biotransformation by N-dealkylation (giving rise to the main active
metabolite DEA), deiodination (giving rise to moniodo-AM, desiodo-AM and desiodo-DEA) and glucuroconjugation (giving rise to glucuro- and arylsulphoconjugated metabolites excreted in the bile). Elimination of AM is mainly with the faeces through biliary excretion of its metabolites, accounting for 65–75% of the ingested drug. AM and DEA are also excreted in sweat, saliva, tears and semen.2

The thyroidal effects of AM can be divided into:

1. obligatory effects—effects observed in every subject treated with AM, resulting in changes of thyroid function tests.
2. facultative effects—effects observed only in a subset of patients treated with AM, resulting in amiodarone-induced hypothyroidism (AIH) or amiodarone-induced thyrotoxicosis (AIT).

In this context, it is relevant that similarities have been observed between the effects of hypothyroidism and of AM treatment. Both conditions induce bradycardia, lengthening of the cardiac action potential and depression of myocardial oxygen consumption. It has therefore been hypothesized that the cardiac effects of AM can be explained—at least partly—by the induction of a ‘local hypothyroid-like condition in the heart’. Indeed, AM treatment is associated with decreased SERCA2a and aMHC and increased bMHC gene expression in the heart, closely resembling the changes in systemic hypothyroidism.6 Mechanisms by which DEA causes changes in the expression of these T3-dependent genes include inhibition of T3 binding to thyroid hormone receptors (TRs), inhibition of co-activator binding to TR and inhibition of TR binding to the thyroid hormone responsive element (TRE).7–10 The findings support the hypothesis of a local hypothyroid-like condition in the heart induced by AM.11 These cardiac effects of AM are apparently obligatory ones, as they are observed irrespective of ambient TSH levels. Another good example of an obligatory effect of AM mediated by TR is the gradual increase of plasma cholesterol from 5.1 ± 0.2 mmol l⁻¹ before treatment to 6.9 ± 0.8 mmol l⁻¹ after 30 months of AM treatment in humans, not related to ambient thyroid hormone or TSH levels.12 The effect has been reproduced in experimental animals, in which the marked increase in plasma low-density lipoprotein (LDL) cholesterol induced by AM could be explained by a significant fall in the gene expression of the LDL receptor in the liver, both at the mRNA and the protein levels.13 LDL receptor gene expression is T3 dependent, mainly mediated by TRb1. AM exerts an inhibitory effect of T3 binding to TRb1, both in vitro and in vivo.7,14

Effect of amiodarone on thyroid function tests

Large amounts of iodine are released into the circulation during biotransformation of the drug. Plasma inorganic iodide rises 40-fold, whereas renal iodide clearance does not change, and 24-h urinary iodide excretion increases to levels between 14,000 and 16,000 μg per 24 h (about 100 times higher than the recommended daily iodine intake of 150 μg for adults by the WHO).15 The thyroid adapts to the iodine excess by acute inhibition of iodine organification; due to this so-called Wolff–Chaikoff effect, T4 and T3 production rates decrease and, consequently, TSH increases (but not exceeding values of 20 mU l⁻¹). Most often, the thyroid escapes from the Wolff–Chaikoff effect; iodine transport is inhibited and absolute iodine uptake in the thyroid (although remaining high) decreases, allowing intra-thyroidal iodine concentrations to fall below the critical level to sustain the Wolff–Chaikoff effect.5,15 After the initial rise of TSH, serum TSH returns to baseline values after 3 months.16 A trend to lower serum TSH has been observed with continued treatment, related to the cumulative dose of AM.2
Furthermore, AM treatment inhibits type 1 deiodinase, resulting in a decreased T3 production rate and an increased rT3 metabolic clearance rate; consequently, serum T3 and fT3 fall by 10–25% and serum rT3 rises by 170%. AM also inhibits T4 transport into the liver, causing a decreased T4 metabolic clearance rate. In later stages, T4 production rate may increase. The altered T4 kinetics results in an increase of serum T4 and FT4 by about 40% (Fig. 2). The changes in serum T4, T3 and rT3 are observed early on in AM treatment and are sustained with prolonged treatment. Reference ranges of serum iodothyronines are thus different from those in normal subjects (Table 1). After discontinuation of AM treatment, it may take 2 months or longer before serum T4 and T3 are normalised. Most studies do not report de novo occurrence of anti-thyroid antibodies during AM treatment.

Fig. 2. Early transient (left column) and late permanent (right column) obligatory effects of amiodarone on thyroid hormone secretion and metabolism. PR, production rate; MCR, metabolic clearance rate; T3R, thyroid hormone receptors; T4S, T4 sulfate; T4G, T4 glucuronide; (+), increase; (−), decrease; ↓, inhibition; ↑, stimulation.
Epidemiology of amiodarone-induced thyroid dysfunction

Incidence and prevalence figures of amiodarone-induced hypothyroidism (AIH) and amiodarone-induced thyrotoxicosis (AIT) vary widely in the literature due to a number of reasons: (1) distinction between subclinical and overt thyroid dysfunction is not always made, (2) reference ranges of serum (free) T4 and T3 are not always adjusted for the use of AM, (3) substantial geographical variations exist due to differences in iodine intake and (4) duration of AM treatment is not always taken into account.

Summarising a number of prospective studies up to 1997 from various countries in which patients were followed up to 4.5 years after starting AM, AIT occurred in 1.7%, 7.9% and 11.9% of patients residing in areas with high, intermediate and low iodine intake, respectively; the corresponding figures for AIH are 13.2%, 5.7% and 6.4%, respectively. The data indicate that (1) overt AIT or AIH will develop in 14–18% of all patients treated with AM, and (2) AIT is more prevalent in iodine-deficient areas, and AIH is more prevalent in iodine-sufficient areas. The predominant effect of ambient iodine intake on the phenotypic appearance of AM-induced thyroid dysfunction is confirmed by recent questionnaire studies: among all patients with AM-induced thyroid dysfunction in North and South Americas (by now a largely iodine-replete continent) 66–63% have AIH and 34% AIT, whereas in Europe (with still many iodine-deplete regions) 25% have AIH and 75% AIT. Other recent follow-up studies show the same picture. A French pharmaco-vigilance study among 98 consecutive patients, treated for the first time with amiodarone, observed 13 cases of hypothyroidism and five cases of thyrotoxicosis in a mean follow-up period of 38 months; the incidence rate for 100 person-years was 4.61 for hypothyroidism and 1.62 for thyrotoxicosis. In a trial from California, patients with persistent atrial fibrillation were randomised to receive AM, sotalol or placebo. At a follow-up of 1–4.5 years, overt hypothyroidism (defined as TSH > 10 mU l⁻¹) had developed in 5.0% of the AM group and in 0.3% of the control group (sotalol + placebo), and subclinical hypothyroidism (TSH 4.5–10 mU l⁻¹) in 25.8% and 6.6%, respectively (overall odds ratio: 4.5, 95% confidence interval (CI): 2.8–7.2). For a TSH value of <0.35 mU l⁻¹, the corresponding figures were 5.3% and 2.4%, respectively; most of these cases were subclinical. In a study from Austria, a previously endemic goitre area, only 44 (61%) of 72 patients had normal thyroid function tests before starting AM; at 8 months follow-up, 16 of the 44 patients had developed (subclinical or overt) AIT, and nine (subclinical or overt) AIH.

Thyroid monitoring during amiodarone treatment

The high incidence of AIT and AIH, and the potential danger of worsening of heart disease upon occurrence of AIT and AIH, seem valid reasons to call for thyroid monitoring in AM-treated patients. Indeed, all guidelines recommend thyroid function tests before and during treatment. The authoritative guideline of the North American Society of Pacing and Electrop-
hysiology recommends TSH and T4 tests at baseline and then every 6 months\textsuperscript{24}, but others recommend to include thyroid antibodies at baseline and to perform follow-up tests more frequently at 1, 3 and 6 months, and then every 3–6 months.\textsuperscript{25} In the absence of studies comparing outcomes of patients managed with different monitoring regimens, it might be helpful to recall a Dutch prospective study in which thyroid function tests were routinely performed at baseline and thereafter every 6 months.\textsuperscript{26} Out of the 58 included patients (all euthyroid at baseline), 47% maintained a normal TSH during follow-up. An elevated TSH was an early event observed in 15%; among them, 66% developed overt AIH (always in the first 18 months of treatment), 17% remained subclinically hypothyroid and 17% finally reverted to overt AIT. TPO-Ab at baseline carried a relative risk of 7.3 (95% CI: 1.45–36.55) for AIH. No new occurrences of thyroid auto- antibodies were observed during follow-up. A suppressed TSH was observed in 38%; among them, 35% developed overt AIT, 18% remained subclinically hyperthyroid and 47% reverted spontaneously to a normal serum TSH. Cases of overt AIT continued to occur during follow-up and could not be predicted: they often had a sudden explosive onset. The probability for maintaining a normal serum TSH at any time point during follow-up is very low (Fig. 3).

Fig. 3. Probability of developing overt thyrotoxicosis or overt hypothyroidism (upper panel) and of developing a decreased or increased TSH response to TRH (equivalent to a suppressed and elevated serum TSH respectively (lower panel) in a prospective study among 58 consecutive patients living in an area of intermediate iodine intake who were euthyroid at the start of amiodarone treatment. (Reproduced with permission from Trip et al (26)).
The implications of these findings for thyroid monitoring during AM treatment are as follows. First, inclusion of TPO-Ab besides TSH in the initial assessment before starting AM seems to be useful. TPO-Ab-positive patients are at high risk for developing AIH and should be followed up closely. With respect to baseline TSH, an already abnormal TSH has obviously a higher risk than a normal TSH, and a TSH within the normal range but higher than 2 mU l⁻¹ carries a higher risk for AIH.¹⁸,²²,²³,²⁶

Second, a normal serum TSH during follow-up does not guarantee that AIT will not develop in the interval to the next visit in view of the often sudden onset of AIT. Third, a suppressed TSH during follow-up does not necessarily mean AIT that has to be treated, because in half of these cases TSH returns spontaneously to normal values. Against this background, we would recommend baseline assessment by TSH and TPO-Ab measurements and follow-up assessments every 6 months by TSH only. The finding of an abnormal TSH qualifies for FT4 measurement. Currently, it can only be assumed that routine monitoring of thyroid function will improve patient outcomes. This might be one reason for poor compliance with the existing guidelines.²⁵,²⁷–²⁹

Amiodarone-induced hypothyroidism (AIH)

Pathogenesis

Epidemiological data indicate that AIH preferentially occurs in (1) regions with sufficient iodine intake, (b) females and (c) subjects with pre-existent TPO antibodies. Males are more often treated with AM than are females (M:F= 2.0:1.0), but AIH develops relatively more often in females (M:F= 1.5:1.0) and older patients.² The presence of TPO-Ab of female sex confers a relative risk (RR) of AIH of 7.3 and 7.9, respectively; if both risk factors are present, the RR increases to 13.5.²⁶ Autoimmune (Hashimoto’s) thyroiditis (which has a higher prevalence in females than in males and in iodine-replete than in iodine-deplete areas) thus predisposes to AIH. Subjects with underlying Hashimoto’s disease are very sensitive to iodine excess and are less likely to escape from the Wolff–Chaikoff effect through down-regulation of the NIS-symporter; persistent inhibition of organification then causes hypothyroidism.¹⁸ The proposed pathogenesis is supported by clinical data showing that (a) AIH develops rather early during AM treatment, typically between 6 and 18 months (Fig. 2), (b) serum concentrations and daily or cumulative doses of AM do not differ between patients remaining euthyroid or developing AIH¹⁸,²⁶, (c) AIH does not remit when AM treatment is continued³⁰ and (d) the organification defect in AIH is much higher than in euthyroid or hyperthyroid patients during AM treatment, as evident from the perchlorate discharge test depicted in Fig. 4.³¹ Whereas thyroidal radioiodine uptake is low in AM treated patients who are euthyroid or thyrotoxic (as expected in view of dilution of the radioisotope in the increased stable iodine pool), it is preserved in AIH. The explanation of this interesting finding is as follows. Inhibition of thyroid iodine transport by iodine excess requires organification of the administered iodine; this inhibition is likely mediated by a specific iodinated lipid, of which the concentration and action vary with the total organic iodine content of the gland. In view of the severe organification defect in AIH, the thyroidal concentration of iodinated lipids will be also low; the extent of the negative feedback in thyroidal iodine uptake will diminish, thereby allowing preservation of radioiodine uptake.³¹

In vitro experiments have shown that AM also exerts iodine-independent inhibition of iodide transport and the TSH–cAMP pathway, probably by direct cytotoxic effects.³²,³³
Diagnosis

The clinical picture of AIH is similar to that of hypothyroidism due to other causes. Goitre is rare, and myxoedema coma is exceptionally rare. Laboratory diagnosis is easy: elevated serum TSH and low FT4. In the first 3 months of AM treatment, TSH can be transiently slightly high.

Treatment

Discontinuation of AM results in euthyroidism after 2–4 months in approximately 60%, but hypothyroidism persisted in about 40% after 5–8 months follow-up; TPO-Ab were present in 25% of the former and in 88% of the latter group. In an attempt to shorten the interval between discontinuation of AM and restoration of euthyroidism, potassium perchlorate (500 mg KClO4 twice daily per os) can be given for 1 month; most patients become euthyroid within 2–3 weeks. As KClO4 acute blocks any further uptake of iodine into the thyroid gland, its favourable therapeutic effect indirectly supports the proposed pathogenesis of AIH: failure to escape from the Wolff–Chaikoff effect.

If AM is continued, subclinical hypothyroidism usually persists. In overt AIH, KClO4 given for 15–45 days under continuation of AM restores euthyroidism, but hypothyroidism always recurs 30–60 days after KClO4 withdrawal. Consequently, it seems most appropriate to treat AIH with L-T4, aiming at normalising TSH. The required L-T4 dose may be higher than in spontaneous hypothyroidism.
Amiodarone-induced thyrotoxicosis

Pathogenesis

Epidemiological data indicate that AIT preferentially occurs in (a) regions with insufficient iodine intake and (b) males (M:F = 3.2:1.0). An early study in an iodine-deficient region demonstrated that development of AIT was associated with a diffuse goitre in 29%, a nodular goitre in 38% and with an apparently normal thyroid gland in 33%. AIT in the setting of a previous thyroid disease has been labelled AIT type 1, and in its absence AIT type 2. Antibodies are not involved in the pathogenesis of either type: de novo occurrence of TSH receptor stimulating antibodies has not been observed, and the incidence of thyroid antibodies in AM-treated patients with diffuse or toxic goitre is similar to that in spontaneous hyperthyroidism.

The pathogenesis of AIT type 1 is similar to that of iodine-induced thyrotoxicosis (IIT), in which exposure to iodine excess reveals existing thyroid autonomy in euthyroid patients with latent Graves’ disease or nodular goitre. It explains the preponderance of AIT in iodine-deficient regions (in which the prevalence of nodular goitre is high) and in males (IIT is more common in males than in females). In subjects accustomed to a high environmental iodine intake, the higher sensitivity of the thyroid gland to generate an iodine-induced turn-off signal for hormone biosynthesis makes the thyroid gland relatively resistant to IIT.

The pathogenesis of AIT type 2 is similar to that of subacute thyroiditis (SAT), in which thyrotoxicosis is due to the release of preformed thyroid hormone into the bloodstream from damaged thyroid follicular epithelium. AM and DEA have (independently from iodine) a direct cytotoxic effect on cultured human thyrocytes. AM disrupts the architecture of the thyroid at a cellular and subcellular level in an experimental animal model, changes akin to the severe follicular damage and disruption observed in thyroids of SAT and AIT type 2 whereas AM-treated euthyroid patients show minimal or no thyroid follicular damage. The ultrastructural changes include an increased number of secondary lysosomes, exhibiting marked lipofuscinogenesis and dilation of the endoplasmic reticulum, with sparing of the mitochondria. Similar changes have been observed in other tissues damaged during AM treatment, and disruption of subcellular organelle function seems to explain the toxic effects of AM. Toxicity increases with exposure time to AM in clinical studies and, at times, is related to the cumulative dose of AM.

Other similarities of AIT type 2 with SAT, supporting the view of AIT type 2 as a drug-induced destructive thyroiditis, are (a) the sudden onset, (b) sometimes the presence of a small painful goitre, (c) low or absent thyroidal radioiodine uptake, (d) frequently a self-limiting course and (d) high incidence of a subsequent subclinical hypothyroid stage. Characteristics of both types of AIT are listed in Table 2. The relative frequency of type 1 has decreased over the past decades, whereas that of type 2 has increased.
The onset of AIT is usually very rapid. AIT patients are older, and more often males, than Graves' hyperthyroid patients (age 68 ± 2 vs. 43 ± 2 years, respectively, female-to-male ratio 0.43:1 vs. 3.5:1, respectively). Many AIT patients are asymptomatic; re-occurrence of cardiac arrhythmias, which previously had been controlled, may suggest the diagnosis. Symptoms at the time of diagnosis include unexplained weight loss in 50%, heavy sweating in 42%, palpitations in 37%, hyperkinesia in 29%, muscle weakness in 27%, heat intolerance in 24%, overall weakness in 12% and diarrhoea in 12%. AIT can develop several months after discontinuation of AM, obviously related to extensive tissue storage and the long half-life of the drug.

Biochemical diagnosis of AIT is based on a suppressed TSH in combination with an elevated FT4; T3 can be elevated or normal. Cases of T4 toxicosis thus do occur. Indeed, the FT4-to-FT3 ratio in AIT (as in IIT and SAT) is much higher than in Graves' hyperthyroidism. Distinction between AIT subtypes is considered to be useful because management of types 1 and 2 is different. Potential discriminative features for subtype classification can be obtained from the history (pre-existent thyroid disease?), physical examination (goitre?), laboratory tests (thyroid antibodies?) and imaging procedures (thyroid scan and ultrasonography) (Table 2). AIT type 1 tends to occur somewhat earlier at a lower cumulative AM dose during AM treatment than does type 2, but the wide overlap renders these features irrelevant for distinguishing subtypes. The prevalence of thyroid antibodies is much higher in type 1 than in type 2, but is still about 8% in type 2. Serum interleukin-6 was originally advocated as a very good discriminator (being much higher in type 2 than in type 1), but subsequent studies have been unable to confirm its value. Other inflammatory markers such as serum C-reactive protein are equally ineffective. Thyroidal radioiodine uptake is low or absent in type 2, but can also be low in type 1, and in one study did not differ at all between both subtypes.

### Table 2

Characteristics of amiodarone-induced thyrotoxicosis (AIT) type 1 and type 2.

<table>
<thead>
<tr>
<th></th>
<th>AIT type 1</th>
<th>AIT type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>Iodine-induced thyrotoxicosis</td>
<td>Destructive thyrotoxicosis</td>
</tr>
<tr>
<td>Preexisting thyroid disease</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td>Usually nodular or diffuse goiter</td>
<td>Sometimes small firm (painful) goiter</td>
</tr>
<tr>
<td>Thyroid antibodies</td>
<td>Can be present</td>
<td>Mostly absent</td>
</tr>
<tr>
<td>Thryoidal RAIU</td>
<td>Low or normal</td>
<td>Low or absent</td>
</tr>
<tr>
<td>Thyroid ultrasound</td>
<td>Diffuse or nodular goiter</td>
<td>Heterogeneous pattern</td>
</tr>
<tr>
<td>Doppler sonography</td>
<td>Normal or increased flow</td>
<td>Decreased flow</td>
</tr>
<tr>
<td><strong>99mTc-sestaMIBI</strong></td>
<td>Clear thyroid retention</td>
<td>No thyroid uptake</td>
</tr>
<tr>
<td><strong>Spontaneous remission</strong></td>
<td>Unlikely</td>
<td>Likely</td>
</tr>
<tr>
<td><strong>Preferred treatment</strong></td>
<td>KClO4 + thionamides</td>
<td>Prednisone</td>
</tr>
<tr>
<td><strong>Subsequent hypothyroidism</strong></td>
<td>Unlikely</td>
<td>Likely</td>
</tr>
</tbody>
</table>

**Diagnosis**

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Assessment of thyroid vascularity by means of colour flow Doppler sonography (CFDS), as originally proposed by Bogazzi et al., reveals a patchy pattern of thyroid vascularity to a markedly increased blood flow in type 1 and an absent blood flow in type 2. The usefulness of CFDS has been confirmed in a number of subsequent studies. Quantification of thyroid gland vascularisation by measuring colour pixel density or systolic peak velocity in the inferior thyroid artery differentiated reasonably well between AIT subtypes (classified according to \textsuperscript{131}I uptake and clinical outcome): the Youden’s index (i.e., sensitivity + specificity–1; maximum value 1.0) was 0.64 and 0.53, respectively. However, Duplex and amplitude Doppler sonography requires sophisticated software. The latest tool has been 99mTc-sestaMIBI scan. Uptake is increased in epithelial cells with high numbers of mitochondria and, consequently, increased MIBI retention occurs in hyper-functioning thyroid tissue. Twenty consecutive AIT patients were classified by the presence of goitre, antibodies, RAIU and CDFS as type 1 in eight patients and type 2 in 10. Clear diffuse MIBI retention was seen in six out of eight type 1 patients, whereas no MIBI uptake was observed in 10 out of 12 type 2 patients. Fair persistent MIBI uptake or rapid washout of MIBI uptake was present in two patients each, who later on were called indefinite AIT (possibly mixed cases). We assessed the diagnostic accuracy in these 20 patients using the author’s cut-off values (given in brackets) for discriminating between types 1 and 2. The Youden’s indices were 0.69 for thyroid volume (> 25 ml), 0.60 for CFDS (pattern >1), 0.80 for 24-h RAIU (> 1%) and 0.80 for MIBI (clear retention). MIBI scans thus are promising, and their usefulness requires further investigation.

In summary, none of the proposed methods accurately discriminates between both AIT subtypes, which apparently require a combination of several methods. It may come as no surprise that 15% of American respondents and 27% of European respondents were unable to make a clear-cut diagnosis of type 1 or type 2 AIT upon presentation of an AIT patient who had undergone both CFDS and RAIU in the diagnostic work-up.

Treatment

Management of AIT can be very challenging for the treating physician and is generally considered as difficult. Whereas some cases are mild, others can be severe with a fatal outcome. Complex drug–drug–disease interactions may occur, notably with warfarin, demanding close surveillance of international normalised ratio (INR) levels. The available treatment options are:

1. Stop AM and wait: Patients with AIT type 1 are still thyrotoxic after 6–9 months, whereas most type 2 patients will become euthyroid in 3–5 months.
2. Anti-thyroid drugs (e.g., carbimazole, methimazole and propythiouracil). Many studies report poor efficacy of anti-thyroid drugs in AIT, which comes as no surprise in view of the well-known decreased efficacy of thionamides in iodide-induced thyrotoxicosis (~AIT type 1) and in subacute thyroiditis (~ AIT type 2).
3. Prednisone: No good data are available for type 1, but in type 2—after stopping AM—prednisone (daily dose ranging from 15 to 80 mg orally for 7–12 weeks) effectively restored euthyroidism in 19 of 22 patients. Early discontinuation of steroids after 2–3 weeks is associated with recurrent thyrotoxicosis. The similarity with the effectiveness of prednisone in SAT is obvious, and it thus became the preferred drug in AIT type 2.
4. Potassium perchlorate: KClO\textsubscript{4} acutely inhibits iodide uptake in the thyroid gland; it reduces intrathyroidal iodine content, rendering the thyroid more sensitive to thionamides.
When –after stopping AM– KClO₄ (daily dose 1000 mg orally for 15–45 days) was added to methimazole, half of type 1 and all of type 2 patients were euthyroid at 2 months.² Where KClO₄ (plus thionamides) has become the preferred treatment option in type 1, its usefulness in type 2 has been less appreciated. Steroids inhibit the in vitro cytotoxic effect of AM on thyrocytes, but KClO₄ exerts the same inhibitory effect, although to a lesser extent.⁴¹ KClO₄ plus thionamides also restore euthyroidism in 4–6 months in type 2 when AM is continued⁵⁷, although it is unknown if the same outcome would have been reached with no treatment in view of the tendency to spontaneous improvement of type 2. No serious side effects (e.g., agranulocytosis) of KClO₄ have been reported so far in AM-treated patients, provided the daily dose is not higher than 1000 mg and given for no longer than 4–6 months.

5. Lithium: In an open study, lithium + PTU normalised thyroid function tests faster than PTU alone (in 4 and 11 weeks, respectively) after stopping AM, but there were just a few patients in this study on mainly type 2 AIT.⁵⁸

6. Iopanoic acid: In a randomised clinical trial, among 12 AIT type 2 patients in whom AM was discontinued, prednisone (starting daily dose 30 mg for 2 weeks, gradually tapered and withdrawn after 3 months) restored euthyroidism more rapidly than iopanoic acid (after 43 ± 34 days and 221 ± 11 days, respectively).⁵⁹

7. Thyroidectomy: Surgery may become an option in AIT patients resistant to medical therapy and in desperate cases. Although the operative risk may be enhanced by the co-existing cardiac disease (the very reason for AM treatment), the results are reassuring. Among 34 AIT patients (32 cases of type 2, mean age 60 years) undergoing total thyroidectomy between 1985 and 2002 in the Mayo Clinic, there were three deaths and 10 complications requiring three re-hospitalisations.⁶⁰ In Brisbane, among 14 AIT patients (13 cases of type 2, mean age 50 years) operated between 1998 and 2005, there were no deaths, but two complications.⁶¹ More recently, minimally invasive thyroidectomy after preparation with iopanoic acid was accomplished safely in eight AIT patients (five cases of type 2).⁶²

8. Radioactive iodine: ¹³¹I therapy was thought to be infeasible in AIT due to low RAIU. Recent studies, however, demonstrate that it can be administered. In two patients with AIT type 1 in whom AM was continued, 24-h RAIU was 3.5% but increased to 24.4% after 2 x 0.1 mg rhTSH i.m.; 30 mCi ¹³¹I was administered and both patients were hypothyroid after 3 months.⁶³ An rhTSH dose in this setting should be applied, however, cautiously.⁶⁴ In four patients with type 2 AIT pre-treated with thionamides and prednisone, 24-h RAIU was <4%; after one dose of ¹³¹I (29–80 mCi), three patients had become hypothyroid and one euthyroid within 6 months.⁶⁵

Management questions to be answered are:

1. Is it necessary to stop AM?

As AM is the immediate cause of AIT, it seems logical to discontinue amiodarone treatment. This, indeed, has been the general recommendation. However, the very nature and severity of the underlying cardiac disease renders discontinuation of AM treatment an unattractive option in many cases and puts the patient at risk for worsening of cardiac arrhythmias; consequently, many cardiologists favour continuation of AM treatment. In view of scattered reports that AM can safely be continued in many instances (at least in AIT type 2) and the awareness that a suppressed TSH may spontaneously revert to normal values in about 50% despite discon-
tinuation of AM, a tendency to continue AM is recently observed.\textsuperscript{66,67} Among respondents to recent questionnaire studies, continuation of AM was thought possible by 11\% in type 1 and by 20\% in type 2 (Table 3).\textsuperscript{19,20} In the absence of randomised clinical trials to clarify this issue, our own bias is to prefer to continue AM in AIT type 2 (in view of its mostly selflimiting course) but discontinue AM in type 1 (in view of its protracted course).

2. Is it necessary to distinguish between type 1 and type 2 AIT?

We think it is because it helps in (a) decision making whether or not to continue AM treatment, (b) selecting a treatment modality that is appropriate from a pathophysiological point of view. Most useful for subtyping are—besides the history and neck palpation—measurement of thyroid antibodies, CFDS, RAIU and possibly 99mTc-sesta MIBI thyroid uptake. One may argue that it is not always possible to label AIT patients accurately as type 1 or type 2, and that mixed cases do occur.\textsuperscript{68} Indeed, 15–27\% of respondents in the questionnaire studies suggested a mixed form of AIT in what was thought a prime example of AIT type 1.\textsuperscript{19,20} There is a priori no valid reason why the occurrence of destructive thyroiditis (type 2) should be restricted to subjects without underlying thyroid disease, and why it should not occur in subjects with diffuse or nodular goitre. On the other hand, labelling those patients with type 1 not responding to KClO4 + anti-thyroid drugs and those with type 2 not responding to steroid as ‘mixed’ cases assumes they are not responding because of errors in subtyping. The assumption may be wrong: there are real treatment failures. The alternative—abandon any effort to label AIT as type 1 or 2, and treat all AIT patients with the triple therapy of KClO4, anti-thyroid drugs and prednisone—has the drawback to expose all patients to possible side effects of three drugs, whereas most patients will be cured with less than three drugs.

Table 3

<table>
<thead>
<tr>
<th>Outcome of questionnaire studies on preferred treatment of amiodarone-induced thyrotoxicosis (19,20).</th>
<th>North America</th>
<th>Europe</th>
<th>Latin America</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Preference to stop AM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>79%</td>
<td>90%</td>
<td>97%</td>
</tr>
<tr>
<td>Type 2</td>
<td>66%</td>
<td>80%</td>
<td>94%</td>
</tr>
<tr>
<td>2. Preferred treatment type 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithyroid drugs alone</td>
<td>65%</td>
<td>51%</td>
<td>62%</td>
</tr>
<tr>
<td>Antithyroid drugs + KClO4</td>
<td>15%</td>
<td>31%</td>
<td>21%</td>
</tr>
<tr>
<td>3. Preferred treatment type 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone alone</td>
<td>62%</td>
<td>46%</td>
<td>52%</td>
</tr>
<tr>
<td>Prednisone + antithyroid drugs</td>
<td>16%</td>
<td>25%</td>
<td>12%</td>
</tr>
</tbody>
</table>

3. Is it always necessary to treat AIT?

As outlined above, many cases of AIT type 2 are self-limiting in nature and may not need treatment if mild and the cardiovascular condition is stable. Smaller thyroid volumes and modest increases of serum FT4 have been identified as predictors of a fast response to steroids in AIT type 2\textsuperscript{69} and may guide an active or expectant policy.
4. What is the preferred treatment algorithm?

First, it is worthy of mention that no randomised clinical trials are available to support any of the proposed treatment algorithms. Second, it is interesting that in Turkey it has been proposed to stop AM therapy and start with KClO₄ + methimazole; if after 1 month FT4 has not normalised or decreased by >50%, prednisone is added. In contrast, in the UK, it is proposed to continue AM and to start with prednisone + carbimazole; if after 2 weeks T3 levels have not decreased, consider KClO₄. The widely divergent algorithms might have to do with a relative preponderance of AIT type 1 in iodine-deficient Turkey, and of AIT type 2 in iodine-sufficient UK. Third, it has not been shown conclusively that prednisone shortens the time to recovery in AIT type 2 as compared to spontaneous recovery by adopting a wait-and-see policy. In an open study by Conen et al. in AIT (without specification of subtypes), there was no difference between patients with or without prednisone treatment in the time to normalise FT4 (98 [53–177] vs. 108 [64–189] days) or TSH (138 [94–220] vs. 141 [90–233] days) (median and inter quartile range); however, baseline FT4 was higher in prednisone-treated patients than in those not receiving prednisone (60 [44–85] vs. 37 [29–63] pmol l⁻¹). In AIT type 2 Italian patients, the median time to normalise FT4 upon prednisone treatment was 30 days (95% CI: 23–37) and to normalise TSH 90 days (95% CI 77–103); baseline FT4 was 50 ± 19 pmol l⁻¹. Preferences among thyroidologists worldwide in treating AIT are listed in Table 3. Our own management algorithm is depicted in Fig. 5. Similarly to other algorithms, it is an arbitrary one but takes into account the best available circumstantial evidence. Not included in the algorithm is the time scale between the various decision points. This will depend very much on the severity of AIT and the cardiac disease. It might be prudent to monitor thyroid function tests every 2 weeks in the first month, and every 4 weeks thereafter to detect improvement or deterioration of AIT. In general, treatment should not be stopped before thyroid function tests are normalised; this usually takes about 3 months.
5. What to do when euthyroidism has been restored?

Once euthyroidism has been restored and AM was discontinued for several months, 22–38% of questionnaire respondents would ablate the thyroid, nevertheless, in case of type 1; in case of type 2, 84–92% would just continue to monitor thyroid function. Periodic assessment of thyroid function seems prudent in view of the high incidence of hypothyroidism after cure of AIT type 2: at a mean follow-up of 38 months (range 6–72), 17% had permanent hypothyroidism occurring 10 months (range: 6–24) after reaching euthyroidism.

In case AM needs to be restarted, prophylactic radioiodine (38–48%) or prophylactic thyroidecotomy (13–28%) is usually recommended for type 1, whereas just monitoring is advised in 61% for type 2. There are no good data to support either view.

When AIT type 2 has been cured with continuation of AM treatment, it carries a risk of recurrences. However, the risk appears to be limited: recurrences were observed in three out of 50 patients, occurring 5, 6 and 8 years after the first episode; recurrences were less severe than the initial event.

Fig. 5. Amsterdam algorithm for the management of amiodarone-induced thyrotoxicosis (AIT). AM, amiodarone; KClO₄, twice daily 500 mg potassium or sodium perchlorate; MMI, once daily 30 mg; I131, high therapeutic dose +/- rhTSH; TAPER, gradually tapering of drug dose to zero. (see original text).
Prognosis

Although treatment of AIT is often difficult and fatalities do occur, euthyroidism can be restored in the majority of cases. However, adverse outcomes in relation to left ventricular dysfunction are reported. Among 60 AIT patients (subtypes not specified; treatment by carbimazole 67%, carbimazole + prednisone 15%, thyroidectomy 18%) in whom AM was stopped, six patients (10%) died before normalisation of FT4. Predictors of mortality were higher age and ejection fraction <30%; sex, FT4 and cumulative AM dose had no predictive value.44 In another study, among 84 AIT patients (possible type 1 in 15 patients; treatment by carbimazole 51%, carbimazole + prednisone 32%, thyroidectomy 10%) in whom AM was stopped, mortality was higher in case of ejection fraction <50% (31% vs. 14%) and the same was true for cardiovascular endpoints (73% vs. 49%). Patients receiving prednisone had a worse outcome than those not receiving prednisone, but initial FT4 was higher in the prednisone group.45 AIT itself seems to contribute to these adverse outcomes. In a retrospective follow-up study among 354 patients treated with AM for 48 months, AIT developed in 57 (type 1 in 5, type 2 in 13 and uncertain type in 35; AM was discontinued in 89%, and treatment was by carbimazole or PTU 83%, prednisone 5%, 131I 9%).73 AIT patients had more major adverse cardiovascular events than patients remaining euthyroid (31.6% vs. 10.7%), mostly driven by a higher rate of ventricular arrhythmia requiring admission (7.0 vs. 1.3%); AIT and ejection fraction <45% were independent predictors of these adverse events (hazard ratios 2.68 and 2.52, respectively). Patients with AIH had a higher risk of myocardial infarction (4.1 vs. 0.4%). All-cause mortality was not different between the groups.

Amiodarone and pregnancy

Iodine excess in pregnancy constitutes a risk for the child. Among 64 neonates exposed to amiodarone in utero, goiter occurred in 3%, transient hypothyroidism in 17%, and mild mental retardation with impaired speech and language skills in a few.74 If it is deemed necessary to treat the mother with AM for life-threatening or refractory arrhythmias, the data are reassuring. However, regular ultrasounds should be performed to detect fetal goiter, which can be treated with intra-amniotic L-T4 therapy. AM and DEA are secreted in breast milk, putting the breast-fed baby at risk for hypothyroidism.

Future developments

It is foreseen that AM will be replaced by analogues that are as effective but better tolerated than AM.70 Dronedarone is structurally related to AM (Fig. 1): it lacks an iodine moiety (and thus the iodine-related side effects of AM), whereas its methane sulphonyl group decreases lipophilicity (so shortening half-life and decreasing tissue accumulation). Dronedarone shares the multichannel blocking and antiadrenergic effects of AM.75 Dronedarone is a selective TRα1 antagonist, but unlike AM – does not inhibit the binding of T3 to TRβ1.14 It might induce a hypothyroid-like condition in the heart, like AM.76 So far, the efficacy of dronedarone has not been compared directly with that of AM. According to two large randomised clinical trials, dronedarone is more effective than placebo for maintenance of sinus rhythm in atrial fibrillation, for reducing the ventricular rate during recurrence of arrhythmia and for reducing the incidence of hospitalisation due to cardiovascular events or death in patients with atrial fibrillation.77,78 The incidence of hyper- or hypothyroidism in the dronedarone group was not higher than in the placebo group in both the trials.
Practice points

• FT4 is slightly increased during amiodarone treatment, but TSH remains normal (except for a small transient TSH increase in the first 3 months).
• TSH monitoring every 6 months during amiodarone treatment is recommended.
• Amiodarone-induced hypothyroidism develops rather early (6–18 months) after starting amiodarone, and is best treated with L-T4.
• Amiodarone-induced thyrotoxicosis (AIT) may occur at any time during amiodarone treatment; its onset is often fast and explosive, due to iodine-induced thyrotoxicosis (type 1) or destructive thyrotoxicosis (type 2).
• Although mixed cases do occur, distinguishing between AIT type 1 and 2 is advised (by thyroid size, thyroid antibodies, thyroid colour-flow Doppler sonography, and possibly 99mTc-sestaMIBI scintigraphy).
• AIT type 1 is best treated with the combination of KClO4 and methimazole, and discontinuation of amiodarone.
• AIT type 2 is preferentially treated with prednisone; discontinuation of amiodarone may not be necessary.

Research agenda

• Prospective studies to evaluate whether risk stratification is helpful in the decision to treat or not to treat AIT.
• Prospective studies in AIT type 1 to evaluate the usefulness of prophylactic thyroid ablation before restarting amiodarone.
• RCT to evaluate whether amiodarone can be continued safely in AIT type 2.
• RCT to evaluate which treatment modality delivers the shortest time to normalization of serum FT4 and TSH in AIT type 2.
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