NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-.

Amiodarone Induced Thyrotoxicosis

Paolo E Macchia, MD, PhD
Dipartimento di Medicina Clinica e Chirurgia, Università degli Studi di Napoli "Federico II"

Kenneth R Feingold, MD
Professor of Medicine, University of California- San Francisco Staff Physician - San Francisco VA Medical Center, Metabolism 111F, VA Medical Center, 4150 Clement St, San Francisco, CA 94121
kenneth.feingold@ucsf.edu
Corresponding author.

Created: December 24, 2018.

CLINICAL RECOGNITION

Patients treated with amiodarone for a cardiac arrhythmia may develop amiodarone Induced thyrotoxicosis (AIT). The risk of AIT is increased in iodine-deficient regions. The incidence of AIT varies greatly (between 0.003% and 10%). AIT occurs in 3% of patients treated with amiodarone in North America, but is much more frequent (up to 10%) in countries with a low iodine dietary intake. In contrast to the other forms of hyperthyroidism, AIT is more frequent in males than in females (M/F = 3/1).

AIT manifests with clinical signs indistinguishable from spontaneous hyperthyroidism, however symptoms and signs of thyrotoxicosis are not apparent in all patients, and may be obscured by an underlying cardiac condition. The reappearance or exacerbation of an underlying cardiac disorder after amiodarone is started, in a patient previously stable, should prompt an investigation into thyroid function for suspected development of AIT. Sometimes worsening of a cardiac arrhythmia with recurrence of atrial fibrillation and palpitations is the only clinical evidence of AIT. The development of angina may also occur. Similarly, unexplained changes in warfarin sensitivity, requiring a reduction in the dosage of this drug, can be the consequence of increased thyroid hormone levels, since hyperthyroidism increases warfarin effects.

AIT may develop early during amiodarone treatment, after many months of treatment, and has even been reported occur several months after amiodarone withdrawal, since amiodarone and its metabolites have a long half-life due to accumulation in several tissues, especially fat.

PATHOPHYSIOLOGY

There are two different forms of AIT, and differential diagnosis between the two forms is critical, since treatments are different.

Type 1 AIT usually occurs in an abnormal thyroid gland (latent Grave's disease, multinodular gland) and is the consequence of increased thyroid hormone biosynthesis due to iodine excess in patients with a preexisting thyroid disorder (Amiodarone contains 37% iodine by weight). Type 1 AIT is more common in iodine deficient regions. Type 2 AIT is a destructive process of the thyroid gland leading to the release of pre-formed hormone. This thyroiditis is an intrinsic toxic effect of amiodarone. Type 2 AIT usually persists for one to three months until thyroid hormone stores are depleted. In most countries Type 2 AIT is more common than Type 1 AIT. Differences between Type 1 and Type 2 AIT are described in table 1. Differentiating between AIT Type 1 and 2 is often very difficult on clinical grounds.

Table 1

Differences between Type 1 and 2 Amiodarone Induced Thyrotoxicosis

	Type 1	**Type 2**
Underlying thyroid disease	Yes (Multinodular goiter, Grave's)	No
Time after starting amiodarone	Short (median 3 months)	Long (median 30 months)
24-hour iodine uptake	Low-Normal (may be high in iodine deficient regions)	Low to Suppressed
Thyroid Ultrasound	Diffuse or Nodular Goiter may be present	Normal or small gland

	Type 1	Type 2
Vascularity on Echo-color Doppler ultrasound	Increased	Absent
T4/T3 ratio	Usually <4	Usually >4
TgAb / TPOAb/ TSI	May be present	Usually absent
Circulating interleukin-6	Normal to high	Frequently markedly elevated

DIAGNOSIS and DIFFERENTIAL DIAGNOSTIC TESTS

To confirm the diagnosis of AIT it is necessary to demonstrate a suppressed serum TSH associated with an increase in serum FT3 and FT4 levels in a patient currently or previously treated with amiodarone. T3 levels may not be as elevated as expected as amiodarone inhibits the conversion of T4 to T3 and severe non-thyroidal illness may be present blocking the increase in T3. The presence of a preexisting thyroid disorder is suggestive for Type 1 AIT. Frequently in patients with Type 2 AIT an increased T4/T3 ratio is present as a feature of destructive thyroiditis. Thyroid antibodies may be present in Type 1 AIT depending upon the underlying thyroid disorder. High levels of thyroglobulin antibodies and TPO antibodies have also been reported in 8% of Type 2 AIT patients. Type 2 AIT develops as an inflammatory process in a normal thyroid and therefore the levels of IL-6 may be markedly elevated.

Color flow Doppler ultrasonography is useful to differentiate between Type 1 and Type 2 AIT. Intra-thyroidal vascular flow is increased in Type 1 AIT (pattern II-III) and reduced or absent in Type 2 (pattern 0).

In many patients with Type 1 AIT the 24-hr iodine uptake is low. In some patients with Type 1 AIT, despite the very high iodine load, a normal or inappropriately elevated 24-hr iodine uptake may be observed, especially if the patients live in an iodine deficient area. Patients with Type 2 AIT typically have a radioactive iodine uptake < 1%.

In a small pilot study, ^{99m}Tc-sestaMIBI was successfully used in the differentiation between Type 1 and Type 2 AIT: uptake remained elevated in Type1 patients while uptake was absent in Type 2 patients.

While the distinction between Type 1 and Type 2 may sometimes be clear, in many patients neither the clinical findings nor the response to treatment clearly indicate whether the patient has Type 1 or Type 2 AIT. Some patients may have a mixed form of AIT.

TREATMENT

AIT may lead to increased morbidity and mortality, especially in older patients with impaired left ventricular function. Thus, in most patients, prompt restoration and stable maintenance of euthyroidism should be achieved as rapidly as possible.

Mild AIT may spontaneously resolve in about 20% of the cases. Type 1 AIT should be treated with high doses of thioamides (20-60 mg/day of methimazole; or 400-600 mg/day of propylthiouracil) to block the synthesis of thyroid hormones (Figure 1). The response to thionamides is often modest due to the high iodine levels in patients taking amiodarone. In selected patients, potassium perchlorate can also be used to increase sensitivity of the gland to thionamides by blocking iodine uptake in the thyroid. $KClO_4$ should be used for no more than 30 days at a daily dose < 1 g/day, since this drug, especially in higher doses, is associated with aplastic anemia or agranulocytosis. Once thyroid hormone levels are back to normal, definitive treatment of the hyperthyroidism should be considered. If thyroid uptake is sufficient (>10%) radioactive iodine can be used. Thyroid surgery is a good alternative. If thyrotoxicosis worsens after initial control, a mixed form Type1-Type 2 should be considered, and treatment for Type 2 AIT should be started.

Type 2 AIT can be treated with prednisone, starting with an initial dose of 0.5-0.7 mg/kg body weight per day and the treatment is generally continued for three months. If a worsening of the toxicosis occurs during the taper, the prednisone dose should be increased. Thioamides are generally not useful in Type 2 AIT.

Because the distinction between AIT Type 1 and 2 is difficult and not always clear, and because some patients have mixed forms of AIT, these therapies for AIT Type 1 and 2 are occasionally combined.

For patients with persistent hyperthyroidism surgery is the optimal choice. Treatment with iopanoic acid (if available), an iodinated cholecystographic agent, at a dose of 500 mg twice/day has been reported to quickly reduce FT3 levels, and can be used in preparation for the surgery. The treatment should be continued for about seven to 10 days after the surgery to prevent the T3 surge after the drug is withdrawn. Propylthiouracil can also be used to inhibit T4>T3 conversion. Beta blockers will be helpful in preparation for surgery.

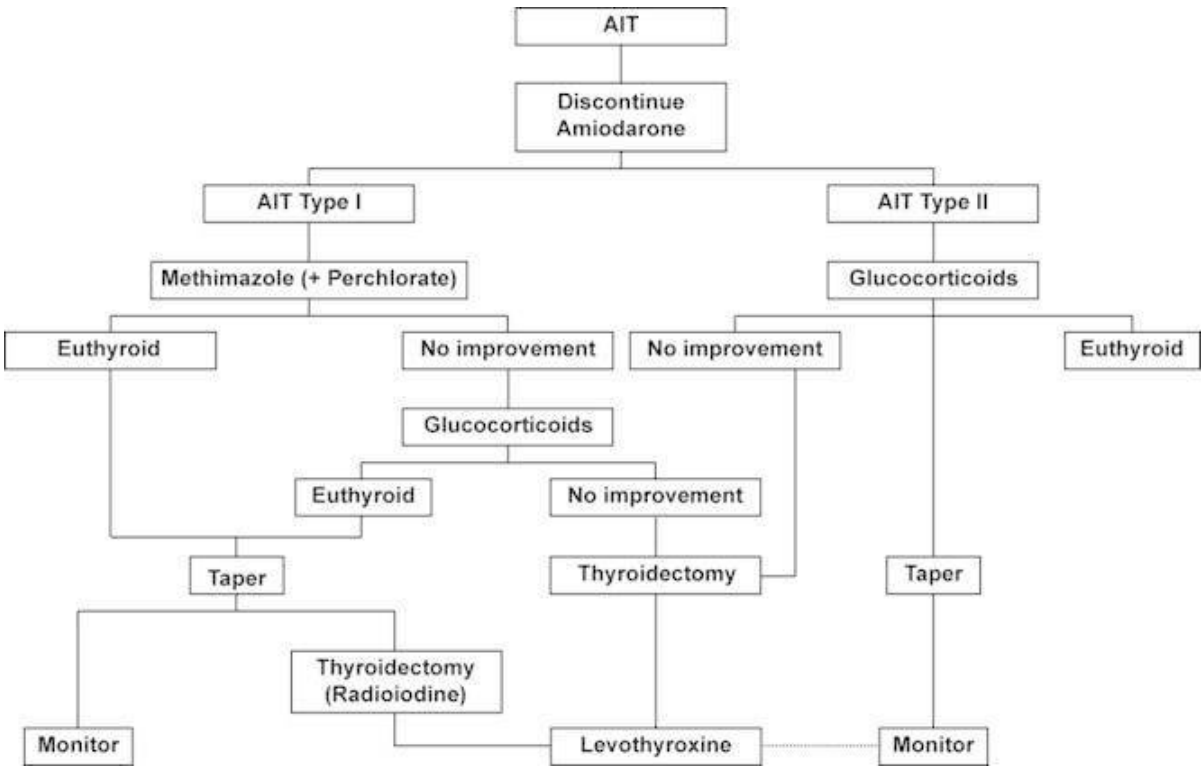

Figure 1.

Management of Patients with Amiodarone Induced Thyrotoxicosis

FOLLOW-UP

It is still debatable whether amiodarone should be discontinued once the diagnosis of AIT is made. Because of the long half-life, there is no immediate benefit in stopping the drug. However, some forms of Type 2 AIT may remit with amiodarone withdrawal. If feasible from the cardiological point of view, it is probably safer to withdraw amiodarone and use a different anti-arrhythmic drug, but no controlled trials have been published on this question. A good alternative to amiodarone in patients with atrial fibrillation and atrial flutter can be dronedarone, but this drug is contraindicated in patients with NYHA Class IV heart failure, or NYHA Class II–III heart failure with a recent decompensation. Some patients with Type 2 AIT may develop hypothyroidism due to thyroid gland destruction.

GUIDELINES

1. Bartalena L, Bogazzi F, Chiovato L, Hubalewska-Dydejczyk A, Links TP, Vanderpump M. 2018 European Thyroid Association (ETA) Guidelines for the Management of Amiodarone-Associated Thyroid Dysfunction. Eur Thyroid J. 2018 Mar;7(2):55–66. [PMC free article: PMC5869486] [PubMed: 29594056]

REFERENCES

1. Kopp P. Thyrotoxicosis of other Etiologies. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Koch C, Korbonits M, McLachlan R, New M, Purnell J, Rebar R, Singer F, Vinik A, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-2010 Dec 1.
2. Bogazzi F, Tomisti L, Bartalena L., Aghini-Lombardi F, Martino E. Amiodarone and the thyroid: a 2012 update. J Endocrinol. Invest. 2012;35:340–48. [PubMed: 22433945]
3. Bogazzi F, Bartalena L, Martino E. Approach to the patient with amiodarone-induced thyrotoxicosis. J Clin Endocrinol Metab. 2010;95:2529–35. [PubMed: 20525904]

4. Cohen-Lehman J, Dahl P, Danzi S, Klein I. Effects of amiodarone therapy on thyroid function. Nat Rev Endocrinol. 2010;6:34–41. [PubMed: 19935743]
5. Trohman RG, Sharma PS, McAninch EA, Bianco AC. Amiodarone and the thyroid physiology, pathophysiology, diagnosis and management. Trends Cardiovasc Med. 2018 Sep 20. pii: S1050-1738(18)30195-6. [PubMed: 30309693]

Bookshelf ID: NBK279030 PMID: 25905259