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# Amiodarone-induced thyrotoxicosis: Diagnostic and therapeutic strategies

## ABSTRACT

Amiodarone causes thyrotoxicosis in 3% of US patients who use it. Two types of amiodarone-induced thyrotoxicosis are recognized, designated type 1 and type 2, based on whether or not the patient had a preexisting thyroid disorder. Distinguishing between the two can be difficult, but it is important for providing appropriate therapy promptly.

## KEY POINTS

Type 1 amiodarone-induced thyrotoxicosis is seen in patients with preexisting or latent thyroid disorders and is caused by unregulated hormonal synthesis. It is treated with thionamides and potassium perchlorate.

Type 2 occurs in patients with a previously normal thyroid and is due to the release of preformed hormone by an inflammatory destruction of the gland. It is treated with corticosteroids.

The two types can be distinguished by clinical, laboratory, and imaging evidence. Color-flow Doppler sonography shows promise as a single reliable tool for early diagnosis.

Patients with mixed or severe forms of amiodarone-induced thyrotoxicosis should be managed with combination therapy, to establish a quick clinical response.

Thyroidectomy is advised for patients with worsening thyrotoxicosis despite all efforts and for those who must be kept on amiodarone but do not respond to aggressive medical treatment.

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

**A**MIODARONE is a uniquely effective antiarrhythmic drug,<sup>1–10</sup> but it is also dangerously rich in iodine. Amiodarone-induced thyrotoxicosis develops in 3% of amiodarone-treated patients in the United States and in 10% of those living in iodine-deficient areas of the world.<sup>11</sup>

We review amiodarone's effects on thyroid function and how best to diagnose and treat amiodarone-induced thyrotoxicosis.<sup>1–4</sup>

## THE USES AND HIGH IODINE CONTENT OF AMIODARONE

Amiodarone is useful in the treatment of:

- Recurrent severe ventricular arrhythmias (for which it is approved by the US Food and Drug Administration [FDA])
- Paroxysmal atrial tachycardia
- Atrial fibrillation
- Maintenance of sinus rhythm after cardioversion of atrial fibrillation.<sup>5,6</sup>

But 37% of amiodarone's mass is organic iodine; each 200-mg tablet contains about 75 mg, 10% of which is released as free iodide.<sup>1,3</sup> With typical daily doses of 1 to 3 tablets a day, the patient is exposed to 7 to 21 mg of free iodide—over 50 times the optimal intake.

## A SPECTRUM OF LONG-LIVED EFFECTS

Amiodarone can cause a spectrum of effects on the thyroid (TABLE 1), which can begin as early as a few weeks after starting treatment or up to 4 years after its continuous use. In fact, because amiodarone accumulates in liver and adipose tissue, it can continue to affect the thyroid many months after it is discontinued<sup>1,12</sup>; total body iodine stores remain increased for up to 9



months after stopping. Amiodarone's estimated elimination half-life is 50 to 100 days.<sup>1</sup>

### Euthyroid patients and nonthyroidal illness

Over half of patients treated with amiodarone have “innocent” changes in thyroid hormone levels, including:

- Slightly elevated serum free thyroxine ( $T_4$ ) levels
- Normal or low total triiodothyronine ( $T_3$ ) levels
- Elevated reverse  $T_3$
- Transiently increased or decreased thyrotropin (TSH) concentrations.<sup>12</sup>

However, most of these patients remain clinically euthyroid, ie, they do not manifest overt hypothyroidism or hyperthyroidism and require no intervention other than monitoring their TSH levels.

This phenomenon is partly explained by amiodarone's effects on thyroid hormone synthesis and metabolism. Amiodarone inhibits type 1 5'-deiodinase enzyme activity, thereby decreasing the peripheral conversion of  $T_4$  to  $T_3$ . In addition, amiodarone decreases the clearance of both  $T_4$  and of reverse  $T_3$ , and can act as a competitive antagonist of  $T_3$ .

### High $T_3$ indicates thyrotoxicosis

Thus, low serum TSH levels in a patient who is apparently euthyroid presents a special problem: although indicative of hyperthyroidism, low TSH is not by itself diagnostic and can also be a manifestation of the sick euthyroid syndrome. In a patient with suspected amiodarone-induced thyrotoxicosis who has low TSH but no clinical signs of hyperthyroidism, high free  $T_3$  levels confirm the presence of amiodarone-induced thyrotoxicosis.<sup>13</sup>

### Amiodarone also causes hypothyroidism

Amiodarone can also cause *hypothyroidism*, indicated by persistently elevated TSH. In fact, in the United States the prevalence of amiodarone-induced thyrotoxicosis is much lower (3%) than that of amiodarone-induced hypothyroidism (22%). However, in iodine-deficient areas such as Tuscany, Italy,<sup>11</sup> amiodarone-induced thyrotoxicosis predominates (10%) over hypothyroidism (5%).

**TABLE 1**

### Signs of amiodarone-induced thyrotoxicosis

#### Cardiac signs (may be absent)

- Sinus tachycardia
- Atrial fibrillation
- Ventricular tachycardia
- Angina
- Heart failure

#### Noncardiac signs

- Unexplained weight loss
- Tremor
- Muscle weakness
- Low-grade fever
- Restlessness
- Enlarging goiter

#### Laboratory signs

- Total and free  $T_4$  levels: increased
- Total and free  $T_3$  levels: increased
- TSH: dramatically decreased

The clinical presentation of amiodarone-induced hypothyroidism is usually subtle, while that of amiodarone-induced thyrotoxicosis can be dramatic, with life-threatening cardiac manifestations.<sup>1-4,7-14</sup>

### ■ SIGNS AND SYMPTOMS

Amiodarone-induced thyrotoxicosis should be suspected in a patient who was previously stable on amiodarone but starts showing signs of cardiac decompensation, sinus tachycardia, atrial fibrillation, ventricular tachycardia, or angina (TABLE 1).<sup>1-4</sup>

However, patients may lack cardiac manifestations of thyrotoxicosis because of amiodarone's intrinsic inhibitory effects on the heart (similar to the actions of beta-adrenergic blockers and calcium channel blockers). Other clinical signs of hyperthyroidism may predominate instead, such as weight loss, tremor, muscle weakness, low-grade fever, restlessness, or an enlarging goiter.

Laboratory tests typically demonstrate:

- Elevated total and free  $T_4$
- Elevated total and free  $T_3$
- Dramatically decreased TSH.<sup>1,12</sup>

**Amiodarone can continue to affect the thyroid months after it is stopped**

TABLE 2

**Amiodarone-induced thyrotoxicosis: Type 1 or type 2?**

FINDING	RELATIVE WEIGHT OF FINDING*	
	TYPE 1 (OVERACTIVITY)	TYPE 2 (INFLAMMATION)
<b>Goiter</b>		
Clearly present (diffuse or nodular)	+2	-1
No or minimal goiter	0	+2
<b>Thyroid autoantibodies &gt; twofold of upper normal</b>		
Antimicrosomal (anti-thyroid peroxidase)	+1	0
Antithyroglobulin	+1	0
Anti-receptor antibodies	+1	0
<b>Radioactive iodine thyroid uptake (24-hour values)</b>		
< 1%	-1	+1
1%–3%	+1	-1
> 3%	+2	-2
<b>Interleukin 6 (IL-6) levels</b>		
> twofold of upper normal	-2	+2
Normal (or minimal elevation)	0	0
<b>Color flow Doppler sonography</b>		
Decreased blood flow (pattern 0)	-2	+2
Normal to increased flow (patterns 1–4)	+2	-2
<b>Satisfactory response to a specific therapeutic trial</b>		
Prednisone 30–40 mg/day alone (within 4 weeks)	-2	+2
Thionamide with or without perchlorate (within 8 weeks)	+2	0
Combination of both modalities of treatment	0	0
<b>TOTAL</b>	—	—

\*Add both columns and compare the two totals: a net difference of +5 or greater strongly supports one specific type of amiodarone-induced thyrotoxicosis over the other; a net difference smaller than +3 does not allow for an accurate differentiation. Weighing of the various pieces of data as proposed here is not based on any specific set of prospectively obtained data. This is only a semiquantitative tool, assembled by one of the authors (C.A.L.), which would require rigorous validation before it can be applied with confidence.

In the US, amiodarone-induced hypothyroid is more common than hyperthyroid

**■ TYPE 1 VS TYPE 2**

While the combination of clinical and laboratory abnormalities confirms the diagnosis of thyrotoxicosis, knowing which type of amiodarone-induced thyrotoxicosis is present is essential to selecting the most appropriate treatment. There are two major types:

**Type 1** affects patients with latent or pre-existing thyroid disorders (such as nodular goiter, diffuse goiter, or Graves disease) and is more common in areas of low iodine intake.<sup>11</sup> It is caused by excessive, uncontrolled synthesis of thyroid hormone by autonomously functioning thyroid tissue in response to iodine (jodbasedow phenomenon).<sup>1-4,11,14</sup>

**Type 2** occurs in patients with previously normal thyroid glands and is caused by a destructive inflammatory thyroiditis, induced by amiodarone or its iodine.<sup>15</sup> The drug exerts direct cytotoxic effects on thyroid follicles and triggers inflammation through mechanisms that are poorly understood. As a result of follicular disruption, preformed thyroid hormones are released.<sup>1-4,15</sup>

Until recently it was nearly impossible to distinguish the two types confidently, and the distinction is still often difficult. Furthermore, mixed forms also occur, further complicating the diagnosis.

But the distinction is important, as specific treatments exist for both types, and choos-

ing the wrong therapy results in ineffective or delayed responses and exposes patients to unjustifiable drug side effects.

Because of uncertainty, empirical combinations of treatments are too often used, especially in patients with severe amiodarone-induced thyrotoxicosis, in an effort to achieve prompt control.

### ■ STRATEGIES TO DISTINGUISH TYPE 1 FROM TYPE 2

More reliable diagnostic tools are clearly needed. Until then, we propose establishing a diagnosis by assigning a relative weight to all available information (TABLE 2).

First, clinicians should try to determine whether there is preexisting thyroid disease, which would indicate type 1:

**Physical examination** may reveal a goiter or exophthalmos.

**Ultrasonography** of the thyroid with abnormal patterns (hypoechoic, nodular goiter) or increased gland size should also raise suspicion of type 1.<sup>1-4</sup>

**Antibody tests** can also be used to identify latent autoimmune thyroid disease (subclinical Graves disease). These include thyroid peroxidase (“microsomal”) antibodies, thyroglobulin antibodies, and thyroid-stimulating immunoglobulin. When positive, they lend support to the diagnosis of type 1 amiodarone-induced thyrotoxicosis. But negative tests do not rule out this diagnosis; this is usually the case in multinodular goiter and in up to 30% of patients with typical Graves disease.

**Radioactive iodine uptake (RAIU) studies** are unreliable in the United States. Normal or elevated values indicate type 1 amiodarone-induced thyrotoxicosis,<sup>16</sup> but this is rarely seen here.<sup>2</sup>

Conversely, values that approach 0% are typical of type 2 amiodarone-induced thyrotoxicosis,<sup>4</sup> as expected in a condition functionally similar to subacute thyroiditis.

But low RAIU values are the norm in the United States. Moreover, they do not necessarily imply type 2 amiodarone-induced thyrotoxicosis,<sup>2</sup> because the uptake of the radioiodine tracer is often inhibited by high intrathyroidal (cold) iodine concentrations, even with

accelerated thyroid activity.<sup>1-4</sup> This causes patients with type 1 amiodarone-induced thyrotoxicosis to often be wrongly classified with type 2 simply because their RAIU values are under 3%.

**Biochemical markers** also provide information, but cannot establish a diagnosis. **Serum thyroglobulin** levels increase with thyroid gland destruction, including type 2 amiodarone-induced thyrotoxicosis. However, they also increase markedly with goiter, whether or not hyperthyroidism or autoimmunity are present.<sup>1</sup> Because thyroglobulin levels increase in both types of amiodarone-induced thyrotoxicosis, and actually can be higher in type 1, they are not useful in the differential diagnosis.

**Interleukin-6 (IL-6)** appears to be a better marker of thyroid gland destruction. IL-6 has been reported as markedly elevated in patients with type 2 amiodarone-induced thyrotoxicosis, and normal or minimally increased in type 1.<sup>17</sup>

However, exceptions to this rule are very common,<sup>2,18</sup> casting doubts on the test's utility. Patients with typical type 2 amiodarone-induced thyrotoxicosis often have unexpectedly low IL-6 levels (perhaps due to variable quality of commercial assays). IL-6 is elevated in commonly coexisting conditions (eg, Graves disease, subacute thyroiditis, nonthyroidal illness, and heart failure), also limiting the test's value for distinguishing the two types.

The usefulness of IL-6 testing is probably confined to:

- Cases in which IL-6 is markedly elevated on the initial presentation of thyrotoxicosis (consistent with type 2 amiodarone-induced thyrotoxicosis), as a way to follow the therapeutic response to glucocorticoids. Reversal of the destructive process (signaled by a decrease of the IL-6 concentration) should precede the correction of the hyperthyroidism.
- Helping explain exacerbations in patients with type 2 amiodarone-induced thyrotoxicosis who are being tapered from glucocorticoids.
- Cases of apparent type 1 amiodarone-induced thyrotoxicosis that recur or fail to respond to treatment that actually are mixed forms of amiodarone-induced thyrotoxicosis.<sup>1-4</sup>

**Low TSH is not by itself diagnostic and can indicate sick euthyroid syndrome**



Color flow Doppler sonography determines the amount of blood flow within the thyroid and provides information about its morphology. Four patterns are recognized:

- Pattern 0: absent vascularity, gland destruction
- Pattern 1: uneven patchy parenchymal flow
- Pattern 2: diffuse, homogeneous distribution of increased flow, similar to Graves disease
- Pattern 3: markedly increased signal and diffuse homogeneous distribution.

Pattern 0 is associated with type 2 and the others with type 1 amiodarone-induced thyrotoxicosis.

Color flow Doppler sonography has shown the most promise as the best tool for the rapid and early diagnosis of type 1 and 2 amiodarone-induced thyrotoxicosis<sup>1,2,10,18</sup>; a recent retrospective review of 37 patients with amiodarone-induced thyrotoxicosis during a 3-year period reported very encouraging results.<sup>18</sup>

### ■ TREATMENT IS DIFFICULT

While mild amiodarone-induced thyrotoxicosis subsides spontaneously in up to 20% of cases,<sup>18</sup> treatment is usually a challenge,<sup>8</sup> especially if the type is uncertain.

Whether to stop amiodarone also poses a dilemma because the patient may need it to control his or her arrhythmia. Even if the drug is immediately stopped, the thyrotoxicosis may not reverse for months because of the drug's long elimination half-life and the large total-body iodine stores. Unless amiodarone is ineffective in controlling the arrhythmia, it is usually continued while treating amiodarone-induced thyrotoxicosis.

The two types of amiodarone-induced thyrotoxicosis are treated differently (TABLE 3; FIGURE 1).

**Type 1**, caused by increased hormonal synthesis, must be treated with a **thionamide**, eg, methimazole 30 mg/day or propylthiouracil 200 to 300 mg/day.

In addition, **potassium perchlorate** competitively inhibits iodine intake by the thyroid and minimizes the intrathyroidal iodine content.<sup>19</sup>

Perchlorate use has enjoyed a resurgence in

**TABLE 3**

### Treatment of amiodarone-induced thyrotoxicosis

#### Type 1

Thionamide (eg, methimazole ~30 mg/day or propylthiouracil ~300 mg/day) for as long as needed

Potassium perchlorate (Perchloracaps 200 mg tablets), no more than 5/day. Stop or taper after 30 days

#### Type 2

Prednisone 30–40 mg/day, taper over 2–3 months

recent years because it can control hyperthyroidism in states of high iodine loads. Its use had virtually ceased in the early 1960s (except for single-dose use in the perchlorate discharge test or as an adjunct to pertechnetate scanning), after seven cases of fatal aplastic anemia were reported worldwide among patients treated for thyrotoxicosis of various etiologies.

It is now clear that perchlorate is extremely effective in conjunction with thionamides for treating type 1 amiodarone-induced thyrotoxicosis, and that it can be used safely, provided that the daily dose is 1,000 mg or less and that the dosage is tapered or stopped after approximately 30 days.<sup>19</sup> Thereafter the thionamide alone can be continued for as long as it is needed.

Perchlorate is difficult to obtain through regular pharmacy channels, and it is not FDA-approved for treating hyperthyroidism. Pharmacists may need to be instructed to purchase perchlorate directly from Mallinckrodt (888-744-1414; www.Mallinckrodt.com).

**Type 2** is treated with a relatively long course of a **glucocorticoid** for its anti-inflammatory and membrane-stabilizing effects.<sup>1,2</sup> Prednisone 30 to 40 mg daily, tapered over 2 to 3 months, is recommended.<sup>8,20</sup> **Lithium**, which inhibits thyroid hormone secretion, has been tried with good results in a relatively small number of patients with presumptive type 2 amiodarone-induced thyrotoxicosis.<sup>20</sup>

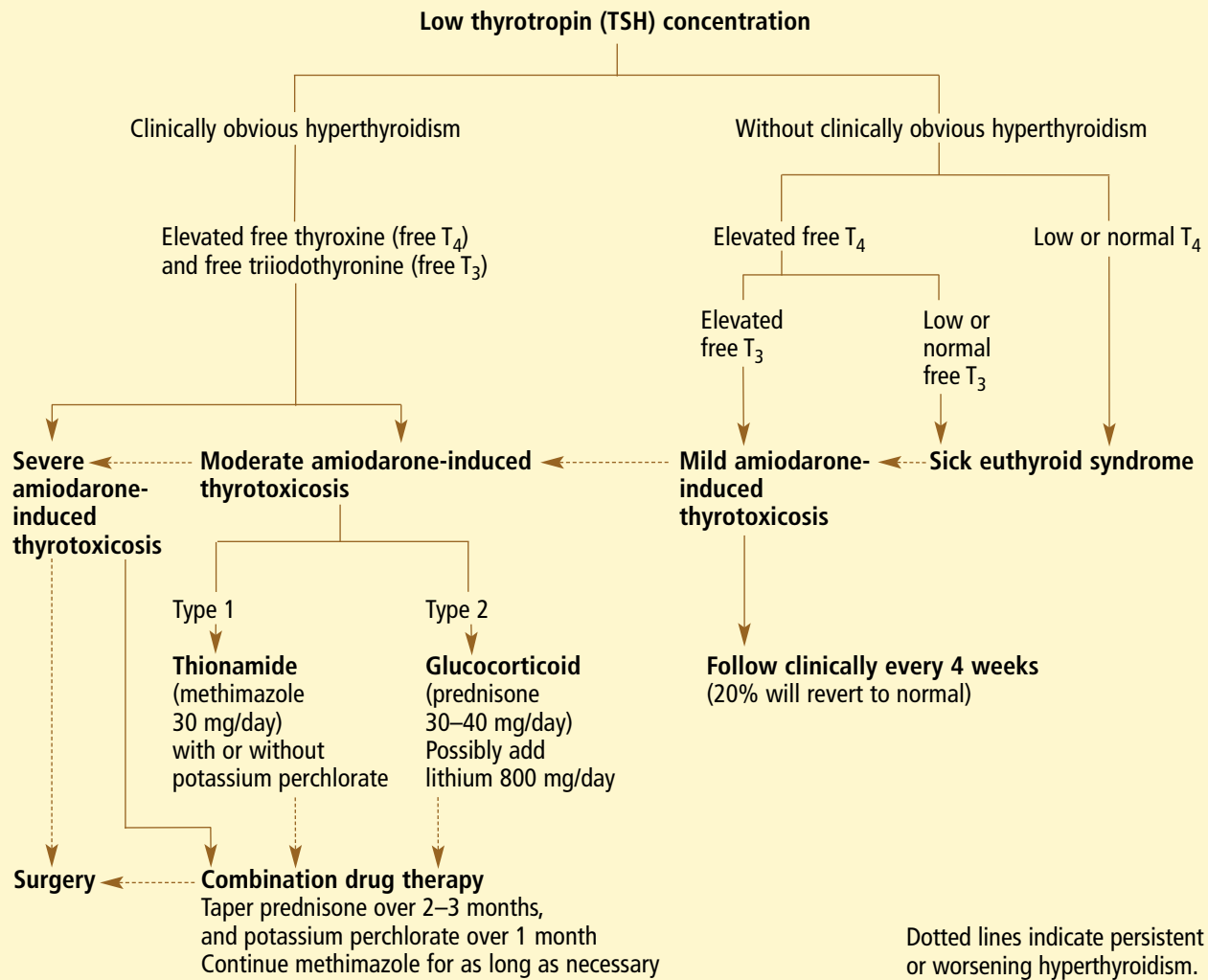
### ■ EXACERBATION AFTER CONTROL

Thyrotoxicosis may worsen after initial control.

**In type 1**, one should evaluate for possible overlapped type 2 amiodarone-induced

**To treat amiodarone-induced thyrotoxicosis, you must know the type**

**Amiodarone-induced thyrotoxicosis: Diagnosis and treatment**



**FIGURE 1.** Mild, moderate, and severe thyrotoxicosis are distinguished by the severity of the clinical picture.

thyrotoxicosis and add steroid therapy to the current treatment.<sup>2,21</sup>

In **type 2**, exacerbation can occur when the corticosteroid treatment is tapered. In such cases, the steroid dose should be increased again.<sup>1,2</sup>

**THYROIDECTOMY, OTHER TREATMENTS**

**Total thyroidectomy** controls thyrotoxicosis and permits amiodarone to be safely continued. It must be considered<sup>22–24</sup> for:

- The most severe cases that fail to respond

to combination therapy with thionamides, perchlorate, and corticosteroids

- Very sick patients who must continue amiodarone.

Total thyroidectomy utilizing local anesthesia may be the best option for the critically ill.<sup>24</sup> The resulting hypothyroidism can be easily treated with thyroid hormone replacement.

**Radioactive iodine** treatment seldom works in amiodarone-induced thyrotoxicosis, because iodine uptake by the gland is inhibited by the iodine of amiodarone. Nevertheless, it can be used as a definitive treatment in the



rare patient with evidence of adequate iodine uptake (high RAIU).<sup>16</sup>

Recombinant TSH could theoretically be used to enhance the uptake of an ablative

dose, but this approach has not been adequately evaluated.

Plasmapheresis has only small or transient beneficial effects.



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