Amiodarone-Induced Thyroid Disease

Rita Nemr, M.D.
Associate Professor of Endocrinology
LAU School of Medicine, Lebanon

SOLFED
Saint Malo May 13, 2017

Byblos
• He who knows syphilis knows medicine
  - Osler

• He who knows amiodarone knows the thyroid
  - Cooper
Amiodarone-Induced Thyroid Disease

Outline

• “Innocent changes” in TFT in normal individuals who take amiodarone

• Type 1 and Type 2 amiodarone-induced thyrotoxicosis

• Amiodarone-induced hypothyroidism
Patient MC

- 67-year-old man with a five-year history of recurrent atrial fibrillation, hypertension, and dyslipidemia
- After several unsuccessful cardioversions for recurrent AF, placed on amiodarone in April 2014
- Converted to sinus rhythm
- Thyroid function monitored periodically
Patient MC

- February 2016 the patient was noted to be back in atrial fibrillation
- Anticoagulation started
- Cardioversion planned, but then deferred because of abnormal thyroid function tests
- Referred for further evaluation
Patient MC

- **Physical exam:** pulse 76, AF. BP 120/70

- The thyroid was approximately two-fold enlarged, firm and nontender. There were no nodules appreciated and no bruits.

- Lungs, heart, abdomen unremarkable
Patient MC

Thyroid function tests

- **April 2014**: TSH 4.5 mU/l
- **July 2014**: TSH 5.4 mU/l
- **October 2014**: TSH 3.5 mU/l
- **March 2016**: TSH < 0.06 mU/l
- **April 2016**: TSH < 0.06 mU/l
  - Free T4 5.13 (0.9-2.0 ng/dl)
  - T3 336 (72-170 ng/dl)
Differential Diagnosis:

- Amiodarone-Induced Thyrotoxicosis
  Type 1 [iodine-induced hyperthyroidism or autoimmune thyroid disease]

vs.

- Amiodarone-Induced Thyrotoxicosis
  Type 2 (amiodarone induced thyroiditis)
Amiodarone pharmacology

- 37% iodine by weight
- One tablet of 200 mg/d yields 75 mg organic iodine
  - Recommended iodine intake is 100-300 mcg/ day
  - 5-10 fold excess
TSH (+) 

Hypothalamus/Pituitary 

T4, T3 (-) 

T4, T3 (-) 

Increase in T4 production 

T3 (+) 

blocks T4 entry into cells 

blocks T3 receptor binding 

blocks T4 to T3 conversion 

blocks intrapituitary T4 to T3 conversion 

Hypothesis/Pituitary 

T4, T3 (-) 

T3 TH Receptor complex bound to regulatory sites on cardiac DNA 

AGCTAGAGTCAT 

T3 (+) 

Liver and other Peripheral tissues 

blocks T3 receptor binding 

blocks T4 to T3 conversion 

blocks T4 entry into cells
Amiodarone Effect on Thyroid Function

3,5,3',5'-Tetraiodothyronine (thyroxine, T₄)

3,5,3'-Triiodothyronine (T₃)

3,3',5'-Triiodothyronine (reverse T₃)

3,3'-Dilodothyronine

TSH
Acute effect of amiodarone on thyroid function
Iervasi et al.
Chronic effects of amiodarone on thyroid function

Melmed et al.
Increase in T4, free T4 **without** hyperthyroidism

- “Innocent” changes in TFT’s can occur in 40%
- Due to a Decreased conversion of T4 $\rightarrow$ T3 (Inhibition of Type’s I + II 5’ - deiodinase)
- T4 levels **Increase** 20-40% during the 1\textsuperscript{st} month, then gradually fall towards baseline
- T3 levels **Decrease** by up to 30% within the 1\textsuperscript{st} few weeks of tx and remain at this level
- TSH levels initially **Increase**, then return to NL in 2-3 months
Amiodarone and the thyroid

• Most patients remain euthyroid while taking amiodarone w. sl $\uparrow$ T4, FT4; sl. $\downarrow$ T3, nl TSH

• In iodine sufficient parts of the world like USA
  – Hypothyroidism:~ 20%, mostly people with underlying (asymptomatic) autoimmune thyroid disease
  – Hyperthyroidism: ~2%

• In iodine insufficient parts of the world just the opposite occurs

• Timing: Hypothyroidism early
  Hyperthyroidism late
Thyroid Function in Amiodarone Treated Patients

- Hypothyroid: 12%
- Euthyroid: 41%
- HyperT4emic: 32%
- Hyperthyroid: 3%
- Subclin. Hypothyroidism: 12%

“Innocent changes”
Amiodarone-induced Hyperthyroidism
Amiodarone-induced thyrotoxicosis: a complex story

- **Type 1: UNDERLYING THYROID DISEASE**
  - Iodine induced (Jod-Basedow phenomenon)
    - Usually in patients with prior *multinodular goiter*
    - Typically occurs after 2-3 years of therapy
  - Less commonly, *Graves’ disease*

- **Type 2: NO UNDERLYING THYROID DISEASE**
  - Amiodarone-related *thyroiditis* (destructive)
    - Usually in patients without prior thyroid disease
    - Typically occurs after 1-2 years of therapy
Amiodarone-induced thyrotoxicosis: clinical

- Usual presentation: weight loss, weakness
  - Goiter may be absent
  - Worsening rhythm disturbance
  - Usually rapid onset
  - Tachycardia may be masked

- PE:
  - AIT Type 1: Thyroid enlarged, nodular
  - AIT Type 2: Thyroid nl. to sl. enlarged; rarely tender
Differences between type 1 and Type 2 amiodarone-induced thyrotoxicosis

Bartalena et al 1995

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>64</td>
<td>63</td>
<td>NS</td>
</tr>
<tr>
<td>Mean free T4</td>
<td>4.1</td>
<td>3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Mean free T3</td>
<td>1.2</td>
<td>1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Mean IL-6</td>
<td>176</td>
<td>440</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Duration of therapy (mo)</td>
<td>51</td>
<td>24</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Thyroid volume (cc)</td>
<td>47</td>
<td>12</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Factor</td>
<td>AIT Type 1</td>
<td>AIT Type 2</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td>Pre-existing thyroid disease</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Thyroid ultrasound</td>
<td>Normal, minimally enlarged</td>
<td>Normal, Decreased</td>
<td></td>
</tr>
<tr>
<td>Radioiodine uptake</td>
<td>Low</td>
<td>Very Low</td>
<td></td>
</tr>
<tr>
<td>Thyroid function tests</td>
<td>Hi T4, T3 normal or high</td>
<td>Hi T4, T3 normal or high</td>
<td></td>
</tr>
<tr>
<td>Color flow Doppler of thyroid</td>
<td>Increased</td>
<td>Normal, Decreased</td>
<td></td>
</tr>
</tbody>
</table>
Amiodarone-induced thyrotoxicosis therapy

- May be very difficult
- Discontinue drug if possible
  - Long half-life (22-55 days in serum) and in fat stores
- Proper treatment depends on underlying diagnosis (type 1 vs. type 2)
Treatment of AIT-Type 1

- Stop amiodarone if possible
- High doses of antithyroid drugs (methimazole 40-80 mg/d) needed and still may be ineffective
  - High intrathyroidal iodide stores
- Perchlorate (500-1000 mg/d)
  - Blocks iodine uptake by the thyroid
  - Aplastic anemia, nephrotic syndrome
- Lithium, may be useful
- Radioiodine may be used in selected cases where radioiodine uptake is high enough
- Plasmapheresis, surgery may be required
Treatment of AIT-Type 1

• Indications for surgery in AIT-type 1
  – Poor response to therapy
  – Discontinuation of amiodarone not possible
  – Life-threatening arrhythmias
Treatment of AIT-Type 2

- Stopping amiodarone may not be necessary
- **Glucocorticoids** mainstay of therapy
  - Prednisone 40 mg/d to begin
  - Taper slowly over months
- Relapses possible with tapering
- May evolve into transient hypothyroidism with rare permanent hypothyroidism
Fig. 3. Serum IL-6 and FT₃ concentrations in a patient with amiodarone-induced thyrotoxicosis without apparent thyroid abnormalities, treated with methimazole (MMI) and then with prednisone (PRED). MMI was discontinued when PRED was begun.
Amiodarone-induced thyrotoxicosis: Mixed Type role of combined therapy

• Some patients have features of both types; combined therapy may be useful **diagnostically**
  – Tapazole 40 mg/d
  – Prednisone 40 mg/d

• If there is rapid response (within 1 week):
  – Most likely AIT Type 2
  – Rapidly taper Tapazole
  – Continue prednisone w. slow taper over months

• If no response after several weeks, consider perchlorate, lithium...........surgery
## Drug Treatment of Amiodarone-Induced Thyrotoxicosis

<table>
<thead>
<tr>
<th></th>
<th>AIT Type 1</th>
<th>AIT Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stop Amiodarone</strong></td>
<td>Yes</td>
<td>Yes (？No)</td>
</tr>
<tr>
<td><strong>Antithyroid Drugs</strong></td>
<td>Methimazole 40-80 mg/d</td>
<td>No</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Lithium, Surgery</td>
<td>?Lithium</td>
</tr>
<tr>
<td><strong>Prednisone</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Radiiodine</strong></td>
<td>Rarely possible</td>
<td>No</td>
</tr>
</tbody>
</table>
Patient MC

- Recurrent AF
- Physical exam: pulse 76, AF. BP 120/70
The thyroid was approximately two-fold enlarged, firm and nontender. There were no nodules appreciated and no bruits.
- TSH <0.06
Free T4 5.13 (0.9-2.0 ng/dl)
T3 336 (72-170 ng/dl)
Diagnosis uncertain:
Other Studies:

- Antithyroid antibodies: negative
- Thyroid stimulating immunoglobulins neg.
- Thyroid ultrasound: “multiple small nodules, with normal blood flow on Doppler”
- 24-hour radioiodine uptake < 0.1%
- IL-6: returned 3 months later
Patient MC

- Presumptive diagnosis of Type 2 amiodarone-induced thyrotoxicosis (thyroiditis) made
- Cardioversion cancelled
- Started on prednisone 40 mg daily
- Plan: repeat thyroid function tests in one week. If no improvement, start Tapazole 40 mg daily
Patient MC: Thyroid Function

<table>
<thead>
<tr>
<th>Date</th>
<th>Free T4 (ng/dl)</th>
<th>TSH mU/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/14</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>4/29</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>5/23</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>5/30</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>6/11</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>6/23</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>7/1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>7/21</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>8/4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>8/25</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>9/22</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Prednisone Dose (mg/d):
- 40
- 30
- 20
- 30
- 15
- 10
- 5

Amiodarone

fT4 normal range:
- 4/14
- 4/29
- 5/23
- 5/30
- 6/11
- 6/23
- 7/1
- 7/21
- 8/4
- 8/25
- 9/22

Free T4

TSH
Patient MC

- Hyperthyroidism resolved over 2 months
- Weight gain on prednisone
- Developed mild (subclinical) hypothyroidism 4 months after presentation
- Cardioverted successfully 11/17/16
Amiodarone-induced Hypothyroidism
Amiodarone-Induced Hypothyroidism

- Occurs in 20% of people in iodine sufficient areas of the world
- Underlying thyroid autoimmunity predisposes to thyroid failure
- Thyroxine doses needed to normalize serum TSH are often higher than would be predicted
  - due to block of intrapituitary T4 to T3 conversion
Mechanisms of autoimmunity to produce iodine-induced hypothyroidism

- Antibody positivity makes thyroid more susceptible to inhibitory effects of iodine
  - Failure to escape from Wolff-Chaikoff effect
  - (Failure to modulate iodide handling)
- But, the majority of patients who become hypothyroid have negative antibodies
Amiodarone-induced hypothyroidism
clinical and laboratory presentation

• Typical hypothyroid symptoms
• Laboratory studies show typical hypothyroidism
• Subclinical hypothyroidism common (10-15%)
• May follow episode of amiodarone induced thyrotoxicosis
• Hypothyroidism can be permanent after the amiodarone is stopped.
Amiodarone-induced hypothyroidism

**Therapy**

- discontinue amiodarone: often not possible
- L-thyroxine
  - dose to normalize TSH may be higher than expected because of inhibition of T4 to T3 conversion within the pituitary
The graph shows the change in TSH levels over time with treatments. The x-axis represents time in years, with increments up to 12 years, and in months, with increments of 2 months. The y-axis represents TSH levels in mU/L, ranging from 0 to 40 mU/L.

- **Amiodarone HCl**: Initially, TSH levels are high, then they show a downward trend, approaching the normal range by the end of the observation period. The dosage is marked as 200 mg.
- **Synthroid**: TSH levels start at a high level and show a gradual decrease, reaching the normal range by the end of the observation period. The dosage is marked as 75 µg, with increments of 100 µg and 112 µg.

The graph is credited to Figge and Dluhy.
Thyroid Management of Amiodarone-Treated Patients

Baseline TSH, fT4, T3, antiTPO Ab; every 6 months check TSH

TSH↑
- Beyond 6 mo.
  - Amiodarone-induced Hypothyroidism
  - Thyroxine

TSH↓
- fT4, T3 normal or minimally increased
  - Monitor closely

- fT4 elevated, T3 elevated or higher than baseline
  - Evaluate to distinguish AIT 1 from AIT 2
  - Treat appropriately

- D/C amiodarone if at all possible
THANK YOU