AMIODARONE AND THYROID

Wilmar M Wiersinga

Department of Endocrinology & Metabolism
Academic Medical Center
University of Amsterdam
The Netherlands
AMIODARONE AND THYROID

OBLIGATORY EFFECTS
= effects observed in every subject treated with amiodarone,
  resulting in changes of thyroid function tests

FACULTATIVE EFFECTS
= effects observed only in a subset of patients treated with amiodarone,
  resulting in amiodarone induced hypothyroidism or thyrotoxicosis
OBLIGATORY EFFECTS OF AMIODARONE ON THYROID

THYROID GLAND

• iodine excess
  
  urinary iodine 150 → 15000 µg/24h
  
  transient TSH↑

PERIPHERAL TISSUES

• inhibition of T4 uptake
  
  FT4↑

• inhibition of 5’-deiodinase
  
  T3↓, rT3↑

• inhibition of T3 binding to thyroid hormone receptors
  
  hypothyroid-like effects
FACULTATIVE THYROID EFFECTS OF AMIODARONE

AMIODARONE-INDUCED HYPOTHYROIDISM (AIH)
- iodine excess

AMIODARONE-INDUCED THYROTOXICOSIS
- iodine excess (AIT type 1)
- destructive thyroiditis (AIT type 2)
  due to cytotoxic effect of amiodarone on thyrocytes
A. BASIC ASPECTS

1. effects on heart
2. effects on liver
3. effects on hypothalamus/pituitary

B. CLINICAL ASPECTS
### Similarity of cardiac effects of amiodarone and hypothyroidism

<table>
<thead>
<tr>
<th>Effect</th>
<th>Amiodarone</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reduction in myocardial oxygen consumption</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lengthening of cardiac action potential</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Effects reversed by thyroid hormone</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
The primary mechanism of action of amiodarone appears to be a “selectively depressant one on cardiac metabolism in parallel, as it were, to thyroxine dependent pathways, an action that would account not only for the drug’s observed effect on myocardial oxygen consumption but also on myocardial repolarization”.

Singh 1980
CHEMICAL STRUCTURES OF AMIODARONE, DRONEDARONE AND METABOLITES

Amiodarone (L3428)

Dronedarone (SR33589B)

Desethylamiodarone (L33520)

Debutyldronedarone (SR35021)
DEA - NONCOMPETITIVE INHIBITOR OF T₃ BINDING TO TRβ1

Rat TRβ1 expressed in E.coli

O.Bakker et al. (1994) Endocrinology 134: 1665
DEA - COMPETITIVE INHIBITOR OF T₃ BINDING TO TRα1

Chicken TRα1 expressed in E.coli

DEBUTYLDRONEDARONE - COMPETITIVE INHIBITOR OF T3 BINDING TO TRα1

Langmuir plot on effect of DBDron on binding of T3 to TRα1

Van Beeren et. al. (2003), Endocrinology 144: 552
DEA = TRα₁ and TRβ₁ ANTAGONIST
DBDRON = SELECTIVE TRα₁ ANTAGONIST

1C 50 values in µM

DEA - TRα₁ 30 ± 3.9, TRβ₁ 71 ± 3.4
DBRON - TRα₁ 59 ± 4.1, TRβ₁ 280 ± 29

AM and DEA concentrations in µmol/kg in human tissues
AM – heart 62, liver 274
DEA – heart 274, liver 3815
TREATMENT OF RATS WITH AMIODARONE OR DRONEDARONE (100 mg/kg/d) for two weeks

<table>
<thead>
<tr>
<th></th>
<th>controls</th>
<th>amiodarone</th>
<th>dronedarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH ng/ml</td>
<td>1.6 ± 0.2</td>
<td>5.8 ± 1.2*</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>T4 nmol/l</td>
<td>81 ± 2</td>
<td>168 ± 6*</td>
<td>85 ± 3</td>
</tr>
<tr>
<td>T3 nmol/l</td>
<td>1.29 ± 0.03</td>
<td>0.85 ± 0.05*</td>
<td>1.25 ± 0.06</td>
</tr>
</tbody>
</table>

* p< 0.005 vs controls and dronedarone
AMIODARONE AND THYROID

A. BASIC ASPECTS
   1. effects on heart
   2. effects on liver
   3. effects on hypothalamus/pituitary

B. CLINICAL ASPECTS
EFFECTS ON THE HEART

• cardiac expression TRα₁ > TRβ₁

• heart rate and QTc are TRα₁ dependent

• hypothesis: similar effects of amiodarone and dronedarone
**EFFECTS ON THE HEART**

<table>
<thead>
<tr>
<th></th>
<th>controls</th>
<th>amiodarone</th>
<th>dronedarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>heart rate (bpm)</td>
<td>382 ± 35</td>
<td>351 ± 23*</td>
<td>390 ± 26</td>
</tr>
<tr>
<td></td>
<td>381 ± 6</td>
<td></td>
<td>296 ± 20*</td>
</tr>
<tr>
<td>QT&lt;sub&gt;C&lt;/sub&gt; interval (msec)</td>
<td>0.114 ± 0.013</td>
<td>0.141 ± 0.018*</td>
<td>0.142 ± 0.023*</td>
</tr>
</tbody>
</table>

p< 0.05 vs controls

(1) van Beeren et al. Endocrinol 2003; (2) Pantos et al. Thyroid 2005
EFFECT OF HYPER/HYPOTHYROIDISM ON T3-DEPENDENT GENE EXPRESSION (ISH) IN RAT HEART

Eu

Hyper

Hypo

αMHC  βMHC  SERCA2a
HYPERTHYROIDISM

\(\alpha\text{MHC} \uparrow \ \beta\text{MHC} \downarrow \ \text{SERCA2a} \uparrow\)

myocardial contractility \(\uparrow\)

HYPOTHYROIDISM

\(\alpha\text{MHC} \downarrow \ \beta\text{MHC} \uparrow \ \text{SERCA2a} \downarrow\)

myocardial contractility \(\downarrow\)

return to fetal programming
EFFECT OF DRONEDARONE/AMIODARONE ON T3-DEPENDENT GENE EXPRESSION (ISH) IN RAT HEART
EFFECT OF DRONEDARONE (90 mg/kg BW/d for 2 wk) ON RAT HEART

<table>
<thead>
<tr>
<th></th>
<th>CONTROLS</th>
<th>DRONEDARONE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-MHC (%)</td>
<td>100±12.8</td>
<td>69±4.6</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>β-MHC (%)</td>
<td>100±6</td>
<td>115±12</td>
<td>NS</td>
</tr>
<tr>
<td>SERCA (%)</td>
<td>100±15</td>
<td>95±18</td>
<td>NS</td>
</tr>
</tbody>
</table>

Pantos et al., Thyroid 2005; 15:16
AMIODARONE (inhibits T3 binding to TRα1 and TRβ1)

- αMHC ↓, βMHC ↑, SERCA2a ↓
- resembles hypothyroidism

DRONEDARONE (inhibits T3 binding to TRα1)

- αMHC ↓, βMHC =, SERCA2a =
- suggests that effect on αMHC is mediated by TRα1
  and effect on βMHC and SERCA2a by TRβ1

Stoykov et al. EJE 2007; 156:695
AMIODARONE AND THYROID

A. BASIC ASPECTS
   1. effects on heart
   2. effects on liver
   3. effects on hypothalamus/pituitary

B. CLINICAL ASPECTS
liver expression TRβ1 > TRα1

LDL receptor and D1 mainly TRβ1 dependent

hypothesis: effects of amiodarone > dronedarone

serum LDL cholesterol (mmol/l):
controls 0.93 ± 0.05
amiodarone 1.15 ± 0.42*
dronedarone 0.86 ± 0.37

* p < 0.05; van Beeren et al. Endocrinology 2003
EFFECTS OF AMIODARONE AND DRONEDARONE ON LIVER D1 AND D3

Van Beeren et al. 2012
EFFECTS OF AMIODARONE AND DRONEDARONE

Van Beeren et al. 2012
AMIODARONE AND THYROID

A. BASIC ASPECTS

B. CLINICAL ASPECTS

1. epidemiology
2. amiodarone – induced hypothyroidism (AIH)
3. amiodarone – induced thyrotoxicosis (AIT)
   a. diagnosis
   b. treatment
   c. prognosis
<table>
<thead>
<tr>
<th>IODINE INTAKE</th>
<th>AIT (HYPER)</th>
<th>AIH (HYPO)</th>
<th>COUNTRY</th>
<th>SAMPLE SIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>1.7%</td>
<td>13.2%</td>
<td>USA, UK</td>
<td>(n=295)</td>
</tr>
<tr>
<td>intermediate</td>
<td>7.9%</td>
<td>5.7%</td>
<td>Spain, Australia, Holland</td>
<td>(n=229)</td>
</tr>
<tr>
<td>low</td>
<td>11.9%</td>
<td>6.4%</td>
<td>Italy, Belgium</td>
<td>(n=419)</td>
</tr>
<tr>
<td>intermediate</td>
<td>8%</td>
<td>6%</td>
<td>The Netherlands 2011</td>
<td>(n=303)</td>
</tr>
</tbody>
</table>
HIGHER PREVALENCE OF AMIODARONE-INDUCED THYROTOXICOSOS (AIT) AND LOWER PREVALENCE OF AMIODARONE-INDUCED HYPOTHYROIDISM (AIT) IN EUROPE THAN IN NORTH AMERICA

INCIDENCE AIT 1.9 AND AIH 1.1 PER 100 PERSON YEARS

Ahmed et al. CE 2011; 75: 388
PREVALENCE OF AMIODARONE-INDUCED THYROTOXICOSIS

Bogazzi et al., Clin Endocrinol 2007
PREDICTABILITY OF AMIODARONE-INDUCED THYROTOXICOSIS (AIT) AND HYPOTHYROIDISM (AIH)

AIT - pre-existent thyroid disease (type 1)
   - high risk
   - no pre-existent thyroid disease (type 2)
     unpredictable, sudden onset

AIH - females with TgAb or TPOAb at risk
   RR 13.5, 95% CI 3.2-57.4

Trip et al., Am J Med 1991
A. BASIC ASPECTS

B. CLINICAL ASPECTS

1. epidemiology
2. amiodarone – induced hypothyroidism (AIH)
3. amiodarone – induced thyrotoxicosis (AIT)
   a. diagnosis
   b. treatment
   c. prognosis
M 63 yr, amiodarone-induced hypothyroidism

QUESTION: HOW TO TREAT AIH?

• history  - amiodarone since 9 months
  - increasing fatigue, mental lethargy, cold intolerance and constipation

• physical exam  - lethargic, hoarse speech
  - blood pressure and pulse rate normal

• lab exam  - ECG: SR, I° AV-block, complete LBBB
  - TSH 55 mU/L, FT4 2.2 pM, TPO-Ab negative.

• thyroid scan  - normal uptake
UNINHIBITED RADIOIODINE UPTAKE IN AMIODARONE-INDUCED HYPOTHYROIDISM

<table>
<thead>
<tr>
<th>Group</th>
<th>TRH-test</th>
<th>Iodine excess</th>
<th>Amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>N</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>II</td>
<td>N</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>III</td>
<td>N,↓</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IV</td>
<td>↓↑</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Graphs showing thyroidal uptake and discharge with different groups and interventions.
EXTRACELLULAR FLUID

THYROID FOLLICULAR CELL

TSH

I⁻

NIS

I⁻

organification

“XI”

iodinated lipid

ClO₄⁻
AMIODARONE-INDUCED HYPOTHYROIDISM
DISCONTINUATION OF AMIODARONE

Van Dam et al., Neth J Med 1993
TREATMENT OPTIONS IN AMIODARONE-INDUCED HYPOTHYROIDISM

1. DISCONTINUE AMIODARONE
   60% euthyroid after 2-4 months
   - mostly no underlying thyroid abnormalities; TPO-Ab in 25%
   40% still hypothyroid after 5-8 months
   - all underlying thyroid abnormalities; TPO-Ab in 88%

2. DISCONTINUE AMIODARONE; ADD KClO4 (1 g/d for 1 month)
   100% euthyroid within 2-3 weeks

3. CONTINUE AMIODARONE, ADD THYROXINE
AMIODARONE AND THYROID

A. BASIC ASPECTS

B. CLINICAL ASPECTS

1. epidemiology
2. amiodarone – induced hypothyroidism (AIH)
3. amiodarone – induced thyrotoxicosis (AIT)
   a. diagnosis
   b. treatment
   c. prognosis
SYMPTOMS AT DIAGNOSIS OF AMIODARONE-INDUCED THYROTOXICOSUS

- 50% unexpected weight loss
- 42% heavy sweating
- 37% palpitations
- 29% hyperkinesia
- 27% muscle weakness
- 24% overall weakness
- 12% diarrhea

Conen et al. J Am Coll Cardiol 2007
REFERENCE VALUES OF THYROID FUNCTION TESTS

<table>
<thead>
<tr>
<th>Test</th>
<th>No Amiodarone</th>
<th>Under Amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH mU/l</td>
<td>0.35-4.3</td>
<td>(0.35-4.3)</td>
</tr>
<tr>
<td>FT4 pmol/l</td>
<td>11-20</td>
<td>12-25</td>
</tr>
<tr>
<td>FT3 pmol/l</td>
<td>3.0-5.6</td>
<td>2.5-5.1</td>
</tr>
<tr>
<td>T3 nmol/l</td>
<td>1.3-3.0</td>
<td>1.0-2.3</td>
</tr>
</tbody>
</table>

Newman et al., Heart 1998
# COMPARISON BETWEEN AIT AND GRAVES’ HYPERTHYROIDISM

<table>
<thead>
<tr>
<th></th>
<th>AIT (n=60)</th>
<th>Graves’ (n=49)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH mU/l</td>
<td>0.06 ± 0.02</td>
<td>0.01 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>FT4 pmol/l</td>
<td>46 ± 3.5</td>
<td>45 ± 4.0</td>
<td>NS</td>
</tr>
<tr>
<td>FT3 pmol/l</td>
<td>8.6 ± 0.7</td>
<td>14.7 ± 1.5</td>
<td>0.002</td>
</tr>
<tr>
<td>FT4/FT3 ratio</td>
<td>7.3 ± 0.5</td>
<td>3.5 ± 0.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>age (yr)</td>
<td>68.3 ± 1.7</td>
<td>42.8 ± 2.3</td>
<td>0.001</td>
</tr>
<tr>
<td>sex (female/male ratio)</td>
<td>0.43 : 1</td>
<td>3.5 : 1</td>
<td>0.001</td>
</tr>
<tr>
<td>time to normalize FT4(days)</td>
<td>195 ± 25</td>
<td>89 ± 10</td>
<td>0.01</td>
</tr>
<tr>
<td>mortality</td>
<td>10 %</td>
<td>0 %</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>AIT TYPE I</th>
<th>AIT TYPE II</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>Physical examination</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>Thyroidal 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>99mTc-sestaMIBI</td>
<td>Clear thyroid retention</td>
<td>No thyroid uptake</td>
</tr>
<tr>
<td>Spontaneous remission</td>
<td>Unlikely</td>
<td>Likely</td>
</tr>
</tbody>
</table>
DIFFERENCES BETWEEN AMIODARONE-INDUCED THYROTOXICOSIS TYPE 1 AND TYPE 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type 1 AIT</th>
<th>Type 2 AIT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>37/33</td>
<td>109/36</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (year)</td>
<td>65 ± 10</td>
<td>63 ± 13</td>
<td>0.4804</td>
</tr>
<tr>
<td>FT4 (pmol/l)</td>
<td>36.50 ± 19.13</td>
<td>44.85 ± 19.67</td>
<td>0.0162</td>
</tr>
<tr>
<td>FT3 (pmol/l)</td>
<td>14.24 ± 9.24</td>
<td>14.63 ± 8.53</td>
<td>0.4273</td>
</tr>
<tr>
<td>FT4/FT3 ratio</td>
<td>3.26 ± 1.50</td>
<td>4.01 ± 1.38</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>AbTg (positive/negative)</td>
<td>25/75</td>
<td>10/125</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>AbTPO (positive/negative)</td>
<td>16/26</td>
<td>8/116</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>TRAb (positive/negative)</td>
<td>25/70</td>
<td>0/145</td>
<td></td>
</tr>
<tr>
<td>Thyroid volume (ml)</td>
<td>47.8 ± 32.6</td>
<td>20 ± 12</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>3 h-RAIU (%)</td>
<td>18 ± 17</td>
<td>2 ± 1.42</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>24 h-RAIU (%)</td>
<td>27.74 ± 21.52</td>
<td>17.73 ± 2.12</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>UIE (mcg/l)</td>
<td>2503.47 ± 3126</td>
<td>6744.8 ± 8359.6</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Cumulative dose amiodarone (g)</td>
<td>74 ± 19.8</td>
<td>121.2 ± 13.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration amiodarone therapy (months)</td>
<td>24.5 ± 34.3</td>
<td>26.1 ± 24</td>
<td>0.0551</td>
</tr>
</tbody>
</table>

Bogazzi et al., Clin Endocrinol 2007
DIFFERENTIAL DIAGNOSIS BETWEEN AIT TYPE 1 AND TYPE 2

1. history
2. palpation of the neck
3. thyroid antibodies
4. thyroid ultrasound
5. thyroid scintigraphy
COLOUR FLOW DOPPLER SONOGRAPHY (CFDS) 
PATTERN OF THYROID VASCULARITY 
(o=absent; I= patchy; II=mild and III= marked increase)
AMPLITUDE DOPPER – COLOUR PIXEL DENSITY (CPD)

PULSED DOPPLER – SYSTOLIC PEAK VELOCITY (SPV)

superior thyroid artery

inferior thyroid artery
<table>
<thead>
<tr>
<th>Metric</th>
<th>AIT TYPE 1 (n = 14)</th>
<th>AIT TYPE 2 (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid volume (ml)</td>
<td>40 ± 34</td>
<td>14 ± 3.9</td>
</tr>
<tr>
<td>CPD (%)</td>
<td>17 ± 21</td>
<td>2.4 ± 2.1</td>
</tr>
<tr>
<td>SPV sup. (cm/s)</td>
<td>39 ± 19</td>
<td>25 ± 7</td>
</tr>
<tr>
<td>SPV inf. (cm/s)</td>
<td>35 ± 18</td>
<td>18 ± 6</td>
</tr>
</tbody>
</table>

Youden index: [sensitivity + specificity] -1
CPD 0.64, SPV sup 0.53, SPV inf 0.53
99 mTc-sestaMIBI THYROID SCAN TO DIFFERENTIATE BETWEEN AIT TYPE 1 AND TYPE 2

- MIBI - increased uptake in epithelial cells with high numbers of mitochondria

- MIBI - increased retention in hyperfunctioning parathyroid and thyroid tissue (Graves’, toxic adenoma)

- 20 consecutive AIT patients, classified by goiter, antibodies, RAIU, CFDS
  8 AIT type 1: 40 mg MMI+1g KClO4 for ≤45 days, then only MMI
  12 AIT type 2: 30-40 mg prednisone, then tapered

99m Tc-sestaMIBI THYROID SCAN IN AIT

clear MIBI diffuse retention in 6 of 8 pat. AIT type 1

faint persistent MIBI uptake in 2 pat. rapid washout of MIBI uptake in 2 pat.

no MIBI uptake in 10 of 12 pat. AIT type 2

<table>
<thead>
<tr>
<th>Vol (ml)</th>
<th>CFDS</th>
<th>RAIU (%)</th>
<th>$^{99m}$TC Scint</th>
<th>MIBI Scint</th>
<th>Initial diagnosis</th>
<th>Final AIT diagnosis</th>
<th>Therapy</th>
<th>Outcome Tot (comb) days</th>
</tr>
</thead>
<tbody>
<tr>
<td>39.5</td>
<td>P1/N2</td>
<td>1</td>
<td>-</td>
<td>+</td>
<td>AIT I</td>
<td>AIT I</td>
<td>+</td>
<td>=</td>
</tr>
<tr>
<td>35</td>
<td>P1/N1</td>
<td>1</td>
<td>-</td>
<td>+</td>
<td>AIT I</td>
<td>AIT I</td>
<td>+</td>
<td>=</td>
</tr>
<tr>
<td>34</td>
<td>P1/N1</td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>AIT I</td>
<td>AIT I</td>
<td>+</td>
<td>=</td>
</tr>
<tr>
<td>38</td>
<td>P1/N1</td>
<td>1</td>
<td>-</td>
<td>+</td>
<td>AIT I</td>
<td>AIT I</td>
<td>+</td>
<td>=</td>
</tr>
<tr>
<td>32</td>
<td>P1/N1</td>
<td>2</td>
<td>-</td>
<td>+</td>
<td>AIT I</td>
<td>AIT I</td>
<td>+</td>
<td>=</td>
</tr>
<tr>
<td>26.2</td>
<td>P0/N1</td>
<td>8</td>
<td>+</td>
<td>+</td>
<td>AIT I</td>
<td>AIT I</td>
<td>+</td>
<td>=</td>
</tr>
<tr>
<td>21.7</td>
<td>P1/N1</td>
<td>2</td>
<td>-</td>
<td>Low</td>
<td>AIT I</td>
<td>AIT Ind</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>26</td>
<td>P0/N0</td>
<td>3</td>
<td>-</td>
<td>+(w)</td>
<td>AIT I</td>
<td>AIT Ind</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>18</td>
<td>P0/N0</td>
<td>0</td>
<td>-</td>
<td>+(w)</td>
<td>AIT II</td>
<td>AIT Ind</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>40</td>
<td>P0/N0</td>
<td>1</td>
<td>-</td>
<td>Low</td>
<td>AIT II</td>
<td>AIT Ind</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>23</td>
<td>P0/N0</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>AIT II</td>
<td>AIT II</td>
<td>=</td>
<td>+</td>
</tr>
<tr>
<td>21.5</td>
<td>P0/N0</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>AIT II</td>
<td>AIT II</td>
<td>=</td>
<td>+</td>
</tr>
<tr>
<td>16.3</td>
<td>P0/N0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>AIT II</td>
<td>AIT II</td>
<td>=</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>P0/N0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>AIT II</td>
<td>AIT II</td>
<td>=</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>P0/N0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>AIT II</td>
<td>AIT II</td>
<td>=</td>
<td>+</td>
</tr>
<tr>
<td>22.9</td>
<td>P0/N0</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>AIT II</td>
<td>AIT II</td>
<td>=</td>
<td>+</td>
</tr>
<tr>
<td>14.7</td>
<td>P1/N0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>AIT II</td>
<td>AIT II</td>
<td>=</td>
<td>+</td>
</tr>
<tr>
<td>15.7</td>
<td>P0/N1</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>AIT II</td>
<td>AIT II</td>
<td>=</td>
<td>+</td>
</tr>
<tr>
<td>32</td>
<td>P1/N0</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>AIT II</td>
<td>AIT II</td>
<td>=</td>
<td>+</td>
</tr>
<tr>
<td>25</td>
<td>P0/N0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>AIT II</td>
<td>AIT II</td>
<td>=</td>
<td>+</td>
</tr>
</tbody>
</table>
# Diagnostic Accuracy of Imaging Procedures for Differentiation Between AIT Type 1 and 2

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Cut-off Value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Youden Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid Volume</td>
<td>&gt; 25 ml</td>
<td>78%</td>
<td>91%</td>
<td>0.69</td>
</tr>
<tr>
<td>Colour Flow Doppler</td>
<td>≥ P1 or ≥ N1</td>
<td>70%</td>
<td>90%</td>
<td>0.60</td>
</tr>
<tr>
<td>24h RAIU</td>
<td>&gt; 1%</td>
<td>100%</td>
<td>80%</td>
<td>0.80</td>
</tr>
<tr>
<td>MIBI</td>
<td>Pos. or low</td>
<td>80%</td>
<td>100%</td>
<td>0.80</td>
</tr>
</tbody>
</table>
AMIODARONE AND THYROID

A. BASIC ASPECTS

B. CLINICAL ASPECTS
   1. epidemiology
   2. amiodarone – induced hypothyroidism (AIH)
   3. amiodarone – induced thyrotoxicosis (AIT)
      a. diagnosis
      b. treatment
      c. prognosis
TREATMENT OPTIONS IN AMIODARONE-INDUCED THYROTOXICOSIS

1. drugs
   * thionamides
   * prednisone
   * perchlorate
   * iopanoic acid

2. surgery
   * total thyroidectomy

3. irradiation
   * $^{131}$I
QUESTIONNAIRE STUDIES ON PREFERRED TREATMENT OF AIT

<table>
<thead>
<tr>
<th>Preferred treatment type 1</th>
<th>North America</th>
<th>Europe</th>
<th>Latin America</th>
</tr>
</thead>
<tbody>
<tr>
<td>thionamides alone</td>
<td>65%</td>
<td>51%</td>
<td>62%</td>
</tr>
<tr>
<td>thionamides + KCl04</td>
<td>15%</td>
<td>31%</td>
<td>21%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preferred treatment type 2</th>
<th>North America</th>
<th>Europe</th>
<th>Latin America</th>
</tr>
</thead>
<tbody>
<tr>
<td>prednisone alone</td>
<td>62%</td>
<td>46%</td>
<td>52%</td>
</tr>
<tr>
<td>prednisone + thionamides</td>
<td>16%</td>
<td>25%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Tanda et al. CE 2008; Diehl et al. CE 2006
TIME TO NORMALIZATION OF THYROID HORMONES IN AIT TYPE 2 TREATED WITH PREDNISONE

- Time to normal T4 and T3 (continuous line): median 30 days (95% CI 23-37)
- Time to normal TSH (dotted line): median 90 days (95% CI 77-103)

FT4 >65 pmol/l and thyroid >20ml associated with longer normalization time.

Bogazzi et al. JCEM 2007
# TIME TO NORMALIZATION OF THYROID HORMONES IN AIT

<table>
<thead>
<tr>
<th></th>
<th>prednisone (n=27)</th>
<th>no prednisone (n=57)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4 pmol/l</td>
<td>60 (44-85)</td>
<td>37 (29-63)</td>
<td>0.004</td>
</tr>
<tr>
<td>time to normal T3 (days)</td>
<td>31 (17-73)</td>
<td>56 (26-64)</td>
<td>NS</td>
</tr>
<tr>
<td>time to normal FT4 (days)</td>
<td>98 (53-177)</td>
<td>108 (64-189)</td>
<td>NS</td>
</tr>
<tr>
<td>time to normal TSH (days)</td>
<td>138 (94-220)</td>
<td>141 (90-232)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conen et al. JACC 2007; values are median with interquartile ranges
RCT OF PREDNISONE 30 mg/d vs iopanoic acid 1000 mg/d in amiodarone-induced thyrotoxicosis type 2

Bogazzi et al., JCEM 2003
RCT OF PREDNISONE 30 mg/d ♦ VS IOPANOIC ACID 1000 mg/d • IN AMIODARONE-INDUCED THYROTOXICOSIS TYPE 2

Bogazzi et al., JCEM 2003
TOTAL THYROIDECTOMY FOR AMIODARONE-INDUCED THYROTOXICOSIS

1. Mayo Clinics, USA
   • 34 pat. (29 M, 5 F), age 60 yr (39-85), 1985-2002
   • 2 type I, 32 type II
   • 3 death, 3 rehospitalization
   • 10 complications

2. Brisbane, Australia
   • 14 pat. (11 M, 3 F), age 50 yr (26-82), 1998-2005
   • 1 type I, 13 type II
   • 0 death
   • 2 complications
131I THERAPY FOR AMIODARONE-INDUCED THYROTOXICOSIS

1) AIT type 1
2 pat., amiodarone continued
24h RAIU at baseline 3.5%, after 2 x 0.1mg rhTSH i.m. 24.4%
30mCi 131I: at 3 months hypo/euthyroid

2) AIT type 2
4 pat., made euthyroid by thionamides and prednisone
24h RAIU < 4%
29-80 mCi 131I: at 6 months hypo/euthyroid

UNRESOLVED QUESTION: IS IT NECESSARY TO STOP AMIODARONE?

<table>
<thead>
<tr>
<th>Preference to stop AIT</th>
<th>North America</th>
<th>Europe</th>
<th>Latin America</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

Tanda et al, CE 2008; Diekl et al. CE 2006
UNRESOLVED QUESTION: IS IT NECESSARY TO DISTINGUISH BETWEEN TYPE 1 AND TYPE 2 AIT?

- YES because treatment differs between type 1 and type 2
- NO because mixed forms of type 1 and type 2 occur (in 15-27% of all AIT cases)
UNRESOLVED QUESTION:
WHAT IS THE PREFERRED TREATMENT ALGORITHM?

AIT n=20
  type I, n=14; type II, n=6

stop amiodarone
MMI 30-50 mg/day
KClO4 1000 mg/day

FT4 N or ↓ >50%
  7 type I, 5 type II
  
  discontinue KClO4

  taper MMI when FT4 N

FT4 not decreased
  7 type I, 1 type II
  
  add prednisone

  taper pred when FT4 N

1 month
4-6 months

Erdogan et al., Thyroid 2003
UNRESOLVED QUESTION: WHAT IS THE PREFERRED TREATMENT ALGORITHM?

AIT: TSH <0.01, ↑T₃

40 mg Carbimazole + 40 mg Prednisolone

After two weeks: Check T₃ levels

T₃ levels: increased/unchanged

Diagnosis: Type I AIT

Stop Prednisolone Continue Carbimazole

Consider adding: Perchlorate ± Lithium

When euthyroid consider: Radioactive iodine Thyroidectomy Long-term Carbimazole

T₃ levels: decreased by >50%

Diagnosis: Type II AIT

Stop Carbimazole Continue Prednisolone

Assess at 3–6 months for hypothyroidism
UNRESOLVED QUESTION:
WHAT IS THE PREFERRED TREATMENT ALGORITHM?

Bogazzi et al. JCEM 2010
**UNRESOLVED QUESTION:**
WHAT TO DO WHEN EUTHYROIDISM HAS BEEN RESTORED?

<table>
<thead>
<tr>
<th>Thyroid ablative therapy?</th>
<th>North America</th>
<th>Europe</th>
<th>Latin America</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>type 1</strong></td>
<td>22%</td>
<td>34%</td>
<td>38%</td>
</tr>
<tr>
<td><strong>type 2</strong></td>
<td>16%</td>
<td>8%</td>
<td>8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>When amiodarone is restarted, prophylactic Tx or 131I?</th>
<th>North America</th>
<th>Europe</th>
<th>Latin America</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>type 1</strong></td>
<td>76%</td>
<td>65%</td>
<td>51%</td>
</tr>
<tr>
<td><strong>type 2</strong></td>
<td>39%</td>
<td>30%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Bartalena et al. CE 2004; Diehl et al. CE 2006; Tanda et al. CE 2008
STUDY AIMS

• To demonstrate the feasibility of continuation of amiodarone in AIT type 2

• To evaluate if perchlorate is useful in AIT type 2
  – given either alone or in combination with prednisone (to shorten time to euthyroidism)
STUDY METHODS

• Randomized multicenter study

• Inclusion criteria:
  1. Amiodarone induced thyrotoxicosis type 2
     – TSH < 0.4 mU/L + FT4 > 25 pmol/L
     – TPO < 100 kU/L, TBII < 2.0 kU/L
     – Poor or no visualisation of thyroid gland on 99mTc-pertechnate scintigraphy
     – No nodular goiter on ultrasound
  2. Continuation of amiodarone treatment

• Exclusion criteria:
  – No informed consent
  – Severe intercurrent illness
STUDY METHODS

- Patients randomized to 3 treatment arms:
  A. 30 mg prednisone/day + 30 mg methimazole/day
  B. 500 mg perchlorate 2x/day + 30 mg methimazole/day
  C. 30 mg prednisone/day + 500 mg perchlorate 2x/day + 30 mg methimazole/day

- In all groups continuation of amiodarone treatment

- Visits every 4 weeks up to 6 months: physical examination + bloodtests. Total follow up 2 yrs.
STUDY METHODS

• If TSH ≥ 0.4 mU/L, medication tapered down to zero dose

• If TSH < 0.4 mU/L after 3 months: continuation of former medication and consider addition of perchlorate 500 mg 2x/day (group A) or prednisone 30 mg/day (group B)

• If thyrotoxicosis persists after 6 months, treatment as seen most appropriate
RESULTS

56 central enrollment via website

42 randomised

14 did not satisfy inclusion/exclusion criteria

36 study population

12 group A

14 group B

10 group C

6 excluded after randomisation
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A prednisone + methimazole</th>
<th>Group B perchlorate + methimazole</th>
<th>Group C prednisone + perchlorate + methimazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex – no (%)</td>
<td>Male 9 (75) 3 (25)</td>
<td>Male 11 (79) 3 (21)</td>
<td>Male 9 (90) 1 (10)</td>
</tr>
<tr>
<td></td>
<td>Female 3 (25)</td>
<td>Female 3 (21)</td>
<td>Female 1 (10)</td>
</tr>
<tr>
<td>Age – yr</td>
<td>54,0 ± 16,7</td>
<td>53,4 ± 13,9</td>
<td>57,0 ± 14,1</td>
</tr>
<tr>
<td>Weight – kg</td>
<td>82,2 ± 23,3</td>
<td>78,3 ± 8,2</td>
<td>84,7 ± 11,5</td>
</tr>
<tr>
<td>Blood pressure – mmHg</td>
<td>Systolic 127 ± 21</td>
<td>126 ± 20</td>
<td>130 ± 23</td>
</tr>
<tr>
<td></td>
<td>Diastolic 74 ± 8</td>
<td>75 ± 9</td>
<td>71 ± 7</td>
</tr>
<tr>
<td>Pulse frequency – beats/min</td>
<td>83 ± 13</td>
<td>74 ± 12</td>
<td>71 ± 14</td>
</tr>
<tr>
<td>TSH – mU/L</td>
<td>0,01 ± 0,03</td>
<td>0,01 ± 0,01</td>
<td>0,01 ± 0,00</td>
</tr>
<tr>
<td>FT4 – pmol/L</td>
<td>60 ± 28</td>
<td>61 ± 25</td>
<td>63 ± 33</td>
</tr>
<tr>
<td>Creatinine – μmol/L</td>
<td>88 ± 21</td>
<td>93 ± 31</td>
<td>94 ± 14</td>
</tr>
<tr>
<td>Glucose – mmol/L</td>
<td>5,1 ± 1,0</td>
<td>5,0 ± 0,8</td>
<td>5,3 ± 0,9</td>
</tr>
<tr>
<td>Hemoglobin – mmol/L</td>
<td>8,8 ± 0,9</td>
<td>9,0 ± 1,4</td>
<td>8,6 ± 0,7</td>
</tr>
<tr>
<td>Leucocytes x10⁹/L</td>
<td>6,9 ± 1,3</td>
<td>7,3 ± 2,2</td>
<td>6,7 ± 1,2</td>
</tr>
</tbody>
</table>

None of the between-group comparisons were significant; values as mean ± SD
# RESULTS – EFFICACY OF TREATMENT FOR THYROTOXICOSIS

<table>
<thead>
<tr>
<th></th>
<th>Group A prednisone + methimazole (N=12)</th>
<th>Group B perchlorate + methimazole (N=14)</th>
<th>Group C prednisone + perchlorate + methimazole (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH ≥ 0.4 mU/L on initial therapy</td>
<td>12 (100%)</td>
<td>10 (71%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Secondary therapy required</td>
<td>0 (0%)</td>
<td>4 (29%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>TSH ≥ 0.4 mU/L on initial + secondary therapy</td>
<td>12(100%)</td>
<td>14 (100%)</td>
<td>10 (100%)</td>
</tr>
</tbody>
</table>
| Time to TSH ≥ 0.4 mU/L median (range) | 8 weeks (4-20)                        | 14 weeks (4-32)                           | 12 weeks (4-28)  
  \[p = 0.5\]                              |
| Amiodarone continued           | 12(100%)                               | 14 (100%)                                | 10 (100%)                                              |

Figures are numbers (%)
## RESULTS – RECURRENT THYROTOXICOSIS

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>prednisone + methimazole</td>
<td>perchlorate + methimazole</td>
<td>prednisone + perchlorate + methimazole</td>
</tr>
<tr>
<td>(N=12)</td>
<td></td>
<td>(N=14)</td>
<td>(N=10)</td>
</tr>
<tr>
<td>Recurrent thyrotoxicosis</td>
<td>N = 1</td>
<td>N = 0</td>
<td>N = 2</td>
</tr>
<tr>
<td>Time of recurrence</td>
<td>24 wks</td>
<td>-</td>
<td>12 and 76 wks</td>
</tr>
<tr>
<td>Treatment</td>
<td>prednisone + methimazole</td>
<td>-</td>
<td>1. methimazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. prednisone + perchlorate + methimazole</td>
</tr>
<tr>
<td>Outcome</td>
<td>TSH ≥ 0.4 mU/L after 8 wks</td>
<td>-</td>
<td>TSH ≥ 0.4 mU/L after 4 wks</td>
</tr>
</tbody>
</table>

Amiodarone continued in all cases
**RESULTS – THYROID FUNCTION AT END OF FOLLOW UP**

<table>
<thead>
<tr>
<th></th>
<th>Group A prednisone + methimazole (N=12)</th>
<th>Group B perchlorate + methimazole (N=14)</th>
<th>Group C prednisone + perchlorate + methimazole (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow up &lt; 2 yr</td>
<td>0</td>
<td>2 († collaps/cardiac transplant)</td>
<td>1 (agranulocytosis on methimazole)</td>
</tr>
<tr>
<td>Follow up 2 yr</td>
<td>12</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Still on amiodarone</td>
<td>12</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>On T₄</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TSH 0.4 – 4.0 mU/L</td>
<td>10</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>&gt;4.0 mU/L</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Figures are number of patients
SIDE EFFECTS MEDICATION

- **Group A** (*prednisone + methimazole*)
  - 1 diabetic patient: increase insulin dose

- **Group B** (*perchlorate + methimazole*)
  - 1 patient muscle pain + high creatine kinase after 2 wks
  - 2 patients nausea

- **Group C** (*prednisone + perchlorate + methimazole*)
  - 1 patient agranulocytosis upon start methimazole for recurrent thyrotoxicosis
  - 1 patient transient elevation of liver enzymes after 12 wks
CONCLUSIONS

• Continuation of amiodarone is feasible in AIT type 2

• Treatment with prednisone is preferable to perchlorate

• Adding perchlorate to prednisone does not shorten time to euthyroidism

• Continuation of amiodarone after successful treatment of AIT type 2 is associated with 3/36 (8.3%) recurrences of overt AIT in 2 yr: recurrences are mild in nature and respond rapidly to treatment in 4-8 wks.

Eskes et al. JCEM 2012
RECURRENCES OF AIT TYPE 2 IN PATIENTS IN WHOM AMIODARONE IS CONTINUED

• in 3 out of 50 patients with AIT type 2
• observed 5, 6 and 8 years after first episode
• recurrence less severe than first episode

Sato et al., Endocr J 2006; 53: 531
DOES CONTINUATION OF AMIODARONE DELAYS RESTORATION OF EUTHYROIDISM IN PREDNISONE-TREATED AIT TYPE 2?

patients collected between 2003-2008

AM continued in 8 pat.
AM discontinued in 32 pat. (matched)

time to normalization of thyroid hormones not different
(24 vs 31 days, NS)

more recurrences under AM continuation
(5/7 vs 3/32, p=0.002)

Bogazzi et al. JCEM 2011
PREFERRED TREATMENT ALGORITHM OF AIT

AIT

type 1
DISCONTINUE AM

worse eu

KClO4+MMI

ADD PREDNISONONE TAPER

worse eu

Tx: 131I TAPER

REGULAR CHECK-UP FOR LATE HYPOTHYROIDISM

type 2
CONTINUE AM

moderate-severe
PREDNISONE+MMI

eu worse

WAIT-AND-SEE

mild

worse eu

TAPER ADD KClO4

STOP AM Tx: 131I
A. BASIC ASPECTS

B. CLINICAL ASPECTS

1. epidemiology

2. amiodarone – induced hypothyroidism (AIH)

3. amiodarone – induced thyrotoxicosis (AIT)
   a. diagnosis
   b. treatment
   c. prognosis
HIGH INCIDENCE OF HYPOTHYROIDISM AFTER TREATMENT OF AIT TYPE 2

• 60 pat. with AIT type 2; amiodarone stopped
• prednisone 30mg/day gradually tapered and withdrawn over 3 months
• mean follow-up 38 months (range 6-72)

• definition of permanent hypothyroidism:
  TSH elevated (with decrease in serum FT4) in 3 subsequent samples after ≥ 6 months from prednisone withdrawal

• incidence of permanent hypothyroidism 17%
  10 months (range 6-24) after reaching euthyroidism
  no baseline differences with those remaining euthyroid

AIT: LEFT VENTRICULAR DYSFUNCTION IS ASSOCIATED WITH INCREASED MORTALITY

- 60 pat. with AIT (no distinction between types 1 and 2; amiodarone stopped
- 67% carbimazole, 15% carbimazole + prednisone, 18% thyroidectomy
- 6 pat. (10%) died before normalization of FT4
- predictors of mortality: age (p=0.005) and severe left ventricular dysfunction (ejection fraction <30%) (p=0.0001)
- sex, FT4, FT3, cumulative amiodarone dose were no predictors

AIT: LEFT VENTRICULAR DYSFUNCTION AND PREDNISONE ARE ASSOCIATED WITH ADVERSE OUTCOME

- 84 pat. with AITD (possible 15 pat. type 1); amiodarone stopped
- 51% carbinazole, 32% carbimazole + prednisone, 10% thyroidectomy

Ejection fraction  
≥ 50%  < 50%

Mortality  
14%  31%*

CV endpoints  
49%  73%ζ
* p = 0.07  ζ p = 0.04

initial FT4 higher in prednisone group

difference in events rate after normalisation of TSH due to arrhythmias (21% vs 41%)
