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Amiodarone-Induced Hyperthyroidism
Diagnosis and clinical course in three adolescents

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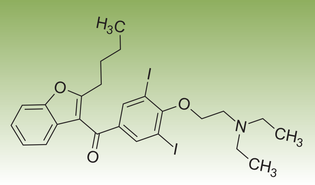
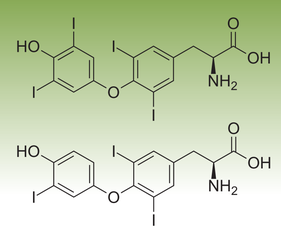
Nothing to disclose



Amiodarone



Thyroxine

Triiodothyronine

Background

- Amiodarone is a potent antiarrhythmic drug
- Side effects are severe affecting various organs (thyroid, lung, liver, eye, skin, etc.)
- In children and adolescents amiodarone is restricted to life-threatening arrhythmias
- **Amiodarone-induced thyroid dysfunction** occurs in 15 - 20% (adult patients)
- Little is known about **amiodarone-induced thyrotoxicosis (AIT)** in pediatric patients

Case 1

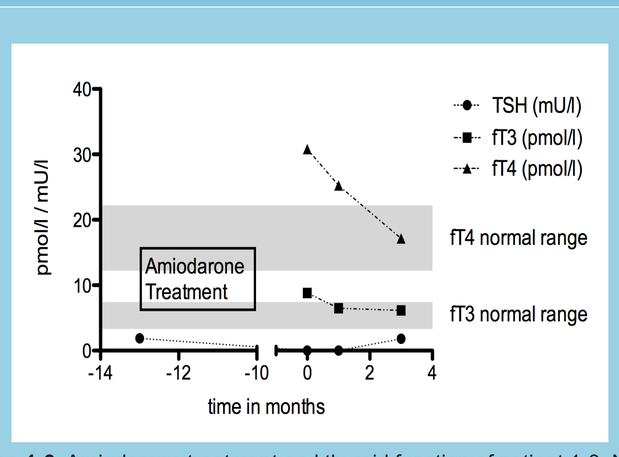
A 17 4/12-year-old male with a surgically corrected **critical aortic valve stenosis** and **sick sinus syndrome**, supplied with an implanted pacemaker, presented with a new episode of atrial flutter. He was treated with **intravenous amiodarone** (150 mg i.v.) and electric cardioversion followed by **amiodarone maintenance treatment** over three months until radiofrequency (RF) catheter ablation.

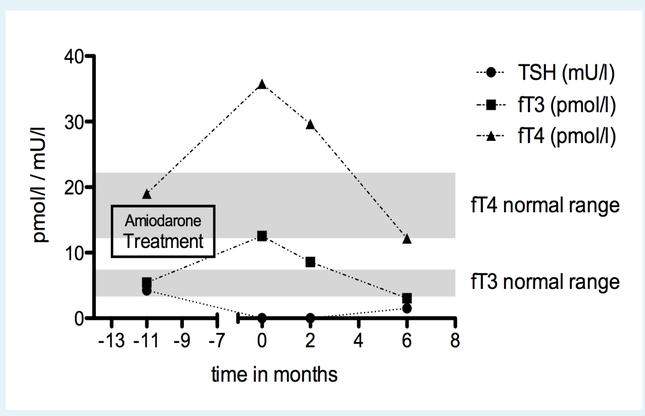
Case 2

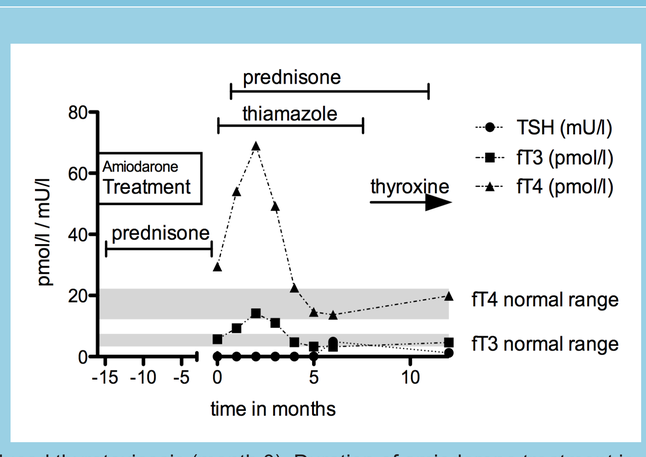
A 13 ½-year-old girl had aggravating palpitations and decreasing physical capacity due to a **focal ventricular tachycardia**. Evaluation revealed a morphologically normal heart structure with mild signs of **biventricular tachycardiomyopathy.** She was started on **intravenous amiodarone**. She underwent three RF catheter ablations and was started on an oral combination therapy with **amiodarone** and metoprolol (2 x 47.5 mg/d) as a rate control therapy. After six months, **amiodarone** was replaced by flecainide.

Case 3

A 16-year-old boy presented to pediatric cardiology with a syncope due to **ventricular tachycardia** occurring after physical exertion. A **chronic myocarditis** was diagnosed and treatment was started with **ramipril and amiodarone**. An implantable cardioverter-defibrillator (ICD) was implanted because of persistent ventricular tachycardia and a cycle of immunosuppressive therapy with prednisone was started. Amiodarone was stopped after one year and prednisone tapered down and stopped three months later.







Figures 1-3. Amiodarone treatment and thyroid function of patient 1-3. Normal ranges are indicated by grey shades. The timeline corresponds to the time of diagnosis of amiodarone-induced thyrotoxicosis (month 0). Duration of amiodarone treatment is indicated by a box, the arrow indicates the current treatment. fT3: free triiodothyronine, fT4: free thyroxine, TSH: thyroid-stimulating hormone.

Manifestation of AIT

One year late re-ablation was planned, due to recurrent atrial flutter, when **hyperthyroidism** was diagnosed. Sodium perchlorate 3 x 400 mg was administered peri- and postoperatively. At presentation in our clinic no typical symptoms of hyperthyroidism were present and fT3 had already normalized. Thyroglobulin antibodies were slightly elevated. Two months later, thyroid function was back to normal values.

Manifestation of AIT

One year later, the girl underwent a fourth and fifth RF catheter ablation. Routine laboratory assessment revealed **hyperthyroidism** at this point. On follow-up visit two months later, TSH was still depressed. Three months later, thyroid function normalized without treatment.

Manifestation of AIT

Because of relapse of ventricular tachycardia a RF catheter ablation was performed and overt **hyperthyroidism** detected. At our outpatient clinic he presented with increased perspiration and sleeping disturbances. Weight was stable. He was on long-term treatment with metoprolol and ramipril. Sonography showed an enlarged hypoechogenic thyroid, consistent with **AIT**. Because of aggravation AIT therapy was started.

Table 1. Clinical Data

	Patient 1	Patient 2	Patient 3
Gender	Male	Female	Male
Age (years)	17.3	13.5	17.3
Previous thyroid disease	none	none	none
Duration of amiodarone treatment	3 months	6 months	12 months
Latency until onset of AIT	10 months	7 months	3 months
Amiodarone Maintenance Treatment	1 x 200 mg 6d/w (3,9 mg/kg)	1 x 200 mg 5d/w (3,8 mg/kg)	1 x 200 mg 5d/w (2,7 mg/kg)
Type of AIT	transient	transient	AIT 2
Duration to resolution of AIT	3 months	3 - 6 months	6 months

Table 1. Clinical data at the time of diagnosis of amiodarone-induced thyrotoxicosis (AIT) of the three patients. AIT 2: type 2 AIT, Tc: technetium 99m, n/a not available.

Table 2. Laboratory Assessment of Thyroid Function

	Patient 1	Patient 2	Patient 3
TSH (mU/l)	**<0.01 -** (0.27-4.2)	**<0.01 -** (0.37-4.2)	**<0.005 -** (0.38-3.47)
fT3 (pmol/l)	**8.83 +** (3.13-6.76)	**12.54 +** (3.13-6.76)	5.7 (3.36-7.41)
fT4 (pmol/l)	**30.82 +** (10.6-22.7)	**35.8 +** (10.6-22.7)	**29.53 +** (12.2-22.2)
anti-TPO antibodies (U/ml)	<5.0 (<34)	n/a	<5 (<34)
anti-TG antibodies (U/ml)	60.9 (<33)	n/a	n/a
anti-TSHR-antibodies (IU/l)	n/a	n/a	<0.9 (<1.8)

Table 2. Thyroid function tests at the time of diagnosis of amiodarone-induced thyrotoxicosis (AIT) of the three patients. + /- indicate if values are above or below normal range. Normal range is indicated in brackets. TSH: thyroid stimulating hormone, TSHR: TSH-receptor, fT3: free triiodothyronine, fT4: free thyroxine, TPO: thyroid peroxidase, TG: thyroglobulin.

Management and Diagnosis of AIT

- Baseline thyroid functions tests (TFT) and autoantibodies before, and TFTs during and after amiodarone treatment - inform your patient about AIT.
- Suppressed TSH and elevated fT4 and fT3 confirm AIT.
- Imaging : Dopplersonography and thyroidal radioiodine uptake may help to differentiate between AIT 1 and 2.
- In asymptomatic patients and stable cardiac function measure TFTs again in 4-6 weeks.
- In severe forms treatment should be initiated with thionamides (+/- sodium perchlorate) in AIT 1 and with oral glucocorticoids in AIT 2.

	AIT 1	AIT 2
Underlying thyroid abnormalities	Yes	Usually no
Colour-flow Doppler sonography	Increased vascularity	Absent hypervascularity
Thyroidal radioiodine uptake	Low/normal/increased	Suppressed
Thyroid autoantibodies	Present if AIT is due to GD	Usually absent
Onset time after starting amiodarone	Short (median 3 months)	Long (median 30 months)
Spontanous remission	No	Possible
Subsequent hypothyroidism	No	Possible
First.line medical treatment	Antithyroid drugs #	Oral glucocorticoids
Subsequent definitve thyroid treatment	Generally yes	No

Table 3. Common features of the two main forms of amiodarone-induced thyrotoxicosis (AIT) from the Guidelines for the Management of Amiodarone-associated Thyroid Dysfunction, Bartalena et al., 2018. AIT 1, AIT type 1, AIT 2 AIT type 2, GD Graves disease. # antithyroid drugs may be associated with sodium perchlorate in the first weeks.

Conclusion:

- Patients, parents and attending physicians should think of thyroid dysfunction as a side effect of amiodarone treatment also in children and adolescents.
- Presentation of AIT might occur during treatment with amiodarone but also after discontinuation.
- Symptoms of AIT might be attributed to the underlying cardiac disease at first, therefore thyroid function tests should be included in the diagnostic work-up.
- Careful endocrine evaluation is necessary in order to start an appropriate therapy in case of persistent AIT.

57ESPE 398-P2

Thyroid

Julia Gesing

Poster presented at: 57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018

PosterSessionOnline.com