

Study protocol

1 Title of the study:

Thyroid density as measured by CT numbers in amiodarone treated patients, in cases of amiodarone induced thyrotoxicosis type 2 (AIT2) and in euthyroid controls (A-Euth).

2 Background:

AIT is a common complication of long term amiodarone treatment with an overall incidence +/- 10%, it appears to occur more frequently in geographical areas with low iodine intake. In a prospective Dutch study AIT occurred in 12.1% of cases (Trip 1991).

Amiodarone is an iodinated derivative of benzofuran that contains two iodine atoms per molecule. Effects on the thyroid are due to iodine load, as well a complex intrinsic effects of amiodarone and its metabolite desethylamiodarone (DEA) on the thyroid gland (Martino 2001).

Amiodarone induced thyrotoxicosis (AIT) is divided in two main types: type 1 AIT and type 2 AIT. Type 1 AIT is iodine induced and occurs in patients with underlying autonomous thyroid gland whereas type 2 AIT is a destructive thyroiditis occurring in patients without underlying thyroid disease. AIT is accompanied by a high morbidity and mortality (Conen 2007) and the actual follow-up scheme of amiodarone treated patients (a regular follow-up of thyroid function tests) is of limited value since the onset of AIT 2 is sudden and explosive (Eskes 2009).

The pathogenesis of AIT type 2 is incompletely understood. In vitro experiments showed a dose dependent thyroid cell toxicity of amiodarone with thyroid follicle disruption. Evidence of in vivo amiodarone-induced follicle cell damage and disruption was demonstrated in specimens from patients treated by thyroidectomy for therapy refractory AIT2 and in autopsy specimens (Brennan 1995). Accumulation of amiodarone and its metabolites represents an important factor for the occurrence of ultrastructural changes indicative of thyroid cytotoxicity (Martino 2001).

The combined excess of iodide, (iodine containing) amiodarone and DEA could result in a prooxidant activity exceeding the endogenous antioxidant capacity (Yamazaki 2007). Therefore a high thyroid iodine concentration could represent a useful marker of a thyroid at risk for AIT 2.

The thyroid iodine *content* as measured by X-Ray fluorescence was significantly higher in AIT patients (with a normal appearing thyroid) than that of amiodarone treated patients who remained euthyroid, however there was overlap (Fragu 1988).

The thyroid iodine *concentration* has not yet been investigated in amiodarone treated patients. Since a significant correlation has been observed between iodine concentration in thyroid tissue and thyroid CT numbers (expressed in Hounsfield Units (HU) (Iida 1983) the thyroid CT number will be studied as a parameter reflecting the thyroid iodine concentration.

3 Aim of the study:

To investigate the thyroid density measured by CT numbers (in Hounsfield Units) in amiodarone treated patients, in cases of amiodarone induced thyrotoxicosis type 2 and in euthyroid controls treated by amiodarone.

4 Patients

AIT 2 group (n° scheduled=15): consecutive patients referred to the endocrinology department for AIT will be evaluated for the presence of AIT type 1 or 2 in order to schedule the correct treatment scheme. The treatment plan for AIT type 2 will consist of methylprednisolone in accordance to the scheme proposed by Bogazzi.

Amiodarone will be withdrawn after approval of the cardiologist.

Inclusion criteria:

AIT type 2 patients defined by

FT4 > 25 pmol/L and TSH < 0.1 mEL, TPO AB < 50 kU/L, TSI < 2E/L,

A normal sized homogeneous thyroid on Ultrasound and a normal or reduced vascularity on colour-flow Doppler ultrasound.

Agreement with the study protocol and signing of the informed consent.

A-Euth group (n° scheduled= 35) : consecutive euthyroid patients on amiodarone, referred to the cardiology department for persistent or recurrent arrhythmia indicating an electrophysiologic study/radiofrequency ablation. Agreement with the study protocol and signing of the informed consent.

Exclusion criteria for both groups:

Concomitant iodine containing medication.

Iodine containing contrast enhanced exams in the preceding 3 months.

5 Procedures:

	AIT2 group	A Euth group
Baseline visit /usual care		
<i>medical history</i>		
duration of amiodarone treatment	x	x
cumulative amiodarone dose calculation	x	x
concomitant medication	x	x
verification of cardiology and radiology listing of the EHR*	x	x
<i>clinical exam including thyroid palpation</i>	x	x
<i>lab</i>		
FT4, FT3, TSH	x	x
TPO-Ab, TSI	x	x
<i>US and CDF</i>	x	o
<i>CT left atrium</i>	o	x
Study procedure		
Thyroid CT number/ limited neck CT without contrast	x	x **

*EHR= electronic health record

**The thyroid CT image will be obtained prior to the standard contrast enhanced cardiac CT preceding the electrophysiologic study.

6 Methods:

For the evaluation of thyroid iodine concentration we obtain 3 slices of the thyroid gland with a 64 slice MDCT (CT 750-HD of General Electronic).

The thyroid density numbers on unenhanced CT are measured on the right and on the left side in normal appearing tissue.

The mean value of the two measurements will be taken into account.

The mean estimated DLP (dose length product) is 50 mGy-cm (estimated effective dose 0.25 mSv).

The thyroid density numbers will be compared using student's t-test. $P < 0.05$ is considered statistically significant.

Normal values for thyroid CT numbers will be calculated from "incidental" thyroid images on enhanced CT scans in patients referred for non thyroid pathology and with a homogeneous normal sized thyroid.

7 Costs & Funding:

For the patients, there will be no costs related to the study.

In the AIT2 group the CT will not be charged (agreement by J. Casselman and J. Delanote); in the A Euth group the slices of the thyroid are obtained during the CT scheduled for usual care, preceding the electrophysiologic study, without additional charge.

8 Data collection

Data will be collected and coded by A Van den Bruel, data analysis by A Van den Bruel, J Delanote, M Duytschaever and R Tavernier

9 References

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10 Investigators

Principal investigator :

A. Van den Briel, endocrinology, (050/452330)

Co-investigators:

M. Duytschaever and R Tavernier, cardiology, (050/452670)

J. Delanote and J. Ghekiere, radiology (050/452100)