Radioiodine therapy in patients with amiodarone-induced thyrotoxicosis (AIT)

Agata Czarnywojtek [1], Rafal Czepczynski [1], Marek Ruchala [1], Ryszard Waśko [1], Magorzata Zgorzalewicz-Stachowiak [2], Ewelina Szczepanek [1], Hanna Zamyslowska [1], Zuzanna Bartkowiak [2], Ewa Florek [3], Jerzy Sowinski [1]

1. Chair and Department of Endocrinology, Metabolism and Internal Medicine;
2. Laboratory of Medical Electrodiagnostics, Department of Health Prophylaxis;
3. Laboratory of Environmental Research, Department of Toxicology;
Poznan University of Medical Sciences, Poland

Correspondence to: Agata Czarnywojtek MD PhD
Department of Endocrinology, Metabolism & Internal Medicine
Przybyszewskiego 49, Poznan 60355, Pol&
TEL: +48 61 8691 330; FAX: +48 61 8691682
E-MAIL: agata.rat@wp.pl

Submitted: 2009-04-24 Accepted: 2009-05-15 Published online: 2009-08-01

Key words: **amiodarone-induced thyrotoxicosis; radioiodine therapy; low radioactive iodine uptake**

Neuroendocrinol Lett 2009; **30**(2):209–214 **PMID:** 19675515 NEL300209A09

Abstract

INTRODUCTION: Amiodarone (AM) is frequently used in the therapy of patients with cardiac disorders. However, due to high iodine content, it has side effects on thyroid function. The use of radioiodine therapy (RIT) in amiodarone-induced thyrotoxicosis (AIT) with low radioactive iodine uptake (RAIU) is still controversial. In these patients therapeutic choices for refractory disease include surgery, antithyroid drugs, or glu ocorticosteriods.

AIM: The aim of the study was to evaluate the efficacy of RIT in patients presenting AIT and low RAIU in two-year follow-up.

PATIENTS AND METHODS: 40 patients (25 men and 15 women) aged from 63 to 83 years (x ± SD: 66.2 ± 5.0 years; median: 65 years) treated with RIT were included into the study. In these patients AM therapy was essential for the underlying heart disorder, while surgery, antithyroid drugs or glucocorticosteroids, were contraindicated. Forty seven patients with toxic multinodular goiter (TMNG) (39 women and 8 men), matched for age (67 ± 12 yr; range 54–89 yr), were enrolled into the study as a comparative group. The diagnostic procedures included baseline thyroid function tests (thyrothropin – TSH, free triiodothyronine – fT_3 and free thyroxine – fT_4 levels), thyroid autoantibodies measurement (antithyroglobulin autoantibodies – TgAb, antithyroid peroxidase autoantibodies – TPOAb, anti-TSH receptor autoantibodies – TRAb), thyroid ultrasonography, thyroid scintiscan and RAIU assessment.

RESULTS: Serum values of TSH, TgAb, TPOAb and TRAb were undetectable in both groups. In patients with AIT fT_4 level was 18.7 to 38.7 pmol/l (mean: 27.1 ± 5.8) and fT_3 concentration was 3.9 to 5.6 pmo/l (mean: 5.7 ± 1.4), while in TMNG patients level of fT_4 was 31.5 to 22.2 pmol/l (mean: 25,3 ± 5,8) and fT_3 concentration was 3.8 to 4,2 pmo/l (mean: 4,2 ± 0,2). Mean RAIU values after 5h and 24h in AIT patients were 2.3 ± 0.5 and 3.1 ± 0.9%, while in TMNG patients were 18,0 ± 3,8 and 35,7 ± 9,1%, respectively. A significant difference ($p<0.001$) between 5h and 24h RAIU in AIT compared to TMNG was noted. In all patients

ORIGINAL ARTICLE

with AIT, a dose of 800 MBq of ^{131}I was administered. During two-year-observation recurrence of hyperthyroidism was observed in two patients (5%) with TMNG. These patients received a second radioiodine dose 16.2 ± 15 months later (the mean re-treatment dose was 735.93 ± 196.1 MBq). In comparison, none of the patients with AIT required a second ^{131}I dose and only one patient (2.5%) 6 months after ablative ^{131}I dose needed anti-thyroid medication. Transient hypothyroidism was observed in only two patients (5%) with AIH, though was not observed in TMNG. During follow-up time, no sudden deaths in AIT patients were observed; one patient was diagnosed with prostate cancer, and in one patient acute toxic hepatitis after AM occurred.

CONCLUSION: RIT may be a safe and useful method of AIT therapy in patients with low RAIU, in whom other treatment methods are contraindicated.

INTRODUCTION

Amiodarone (AM) is an iodine derivative of benzofuran. It belongs to the 3rd class of antiarrhytmic drugs (McEvoy 2000; Reiffel *et al.* 1994) and is commonly used in atrial and ventricular tachyarrhythmias. It also prevents sudden cardiac death (Podrid 1995; Reiffel *et al.* 1994). Each 200 mg tablet contains 75mg of iodine, which by metabolism releases 7–21mg of iodine daily (Kennedy *et al.* 1989). Due to its lipophylic properties, beside thyrocytes, AM and its metabolites accumulate in fat tissue, skeletal and cardiac muscles (Latini *et al.* 1984). The complex mechanism of AM influence on the thyroid, pituitary-thyroid axis and thyroid hormone metabolism includes immunogenic and proinflammatory activity (Martino *et al.* 2001; Wiersinga 1997). By realeasing excess iodine, it favours development of autoimmunological diseases of the thyroid. It causes hypothyroidism in patients with disordered Wolff-Chaikoff phenomenon and subsequently induces apoptosis of thyrocytes (Martino *et al.* 1984; Roti *et al.* 1993).

The pathogenesis of amiodarone-induced thyrotoxicosis (AIT) is not entirely known. However, thyroid function disorder occurs in about 20% of AM treated patients, both at the time of therapy or even several months after cessation of this medication (Bogazzi *et al.* 2001; Martino *et al.* 1987). In case of AIH, the preferred choices of treatment are anti-thyroid drugs (Bartalena *et al.* 1994; 2004; Reichert & Rooy 1989), glucocorticosteroids (Bartalena *et al.* 1996; 2002; 2004), iopanoic acid (Bogazzi *et al.* 2002), or thyroidectomy (Farwell *et al.* 1990; Meurisse *et al.* 1993). In some cases, however, radioiodine therapy (RIT) is also considered. It concerns patients with AM intolerance, cardiac contraindications to surgery, or poor patient's compliance. Obviously, low iodine uptake (RAIU) found in all patients treated with AM makes RIT a questionable method. There is a need for the evaluation of a possible role of RIT in patients with AIT and contraindications to other treatment modalities.

The objective of this study was to assess the clinical efficacy of RIT in patients with AIT.

PATIENTS AND METHODS

Patients. We conducted a retrospective analysis of 40 patients with AIT (25 men and 15 women, aged from 63 to 83 years; mean: 66.2 ± 5.0 years; median: 65 years) who were treated with RIT. The patients received AM due to cardiac arrhythmia. 34 patients suffered from cardiac failure (NYHA functional class < II with left ventricular ejection fraction ≥ 40%) and six patients had low left ventricular ejection fraction <20% and NYHA functional class ≥ III. The patients had never exhibited hyperthyroidism previously.

The diagnosis of AIT was based on the following criteria: history of AM treatment for at least one month, signs and symptoms of hyperthyroidism confirmed by increased free thyroxine (T_4) and suppressed thyrotrophin (TSH) levels that occurred during therapy, a negative titer of circulating thyroid autoantibodies [antithyroglobulin (TgAb), antithyroid peroxidase (TPOAb), anti-TSH receptor (TRAb) autoantibodies] and thyroid of normal or slightly increased volume without relevant nodules (≥1 cm) at conventional ultrasonography.

The history revealed that agranulocytosis occurred in 6 patients, hepatic failure in 8 patients after less than a two-month-period of anti-thyroid therapy. In the remaining cases the best solution was thyroidectomy, however surgery was contraindicated due to advanced heart failure, or refusal of consent.

Methods. The hormonal assessment was performed using Hitachi Cobas e601 chemiluminescent analyzer (Roche Diagnostics). Autoantibodies concentration was assessed by radioimmunological method with the use of commercially available BRAMHS anti-TPO, anti-Tg and TRAK RIA kits and a scintillation gamma-counter (LKB Wallac CliniGamma 1272). Serum TSH concentration was measured with a third-generation sensitivity ≤ 0.005 μIU/mL. The normal ranges for serum hormone concentrations in our laboratory were as follows: free T_4: 11,5–21,5 pmol/l, free T_3: 3,9 – 6,8 pmol/l, TSH: 0,27–4,2 μIU/ml, TRAb <2 IU/l, TgAb <60 IU/ml and TPOAb < 60 IU/ml. In all patients, smokers and non-smokers, the urine cotinine concentration was measured (Costagliola *et al.* 1999; Florek *et al.* 2003).

Sonography. Thyroid ultrasonography was performed with the use of 7.5–17 MHz linear probe using the ALOKA SSD 3500 SV instrument. The thyroid volume was measured by the mean of elliptical shape volume formula (π/6×length×width×depth).

RAIU and scintigraphy. RAIU values were measured 5h and then 24h after the administration of a tracer dose (ca. 2MBq of ^{131}I). The thyroid scintiscan was performed 30 min. after i.v. administration of 150 MBq of ^{99m}Tc. Images were obtained using Nucline gamma camera (Medisco, Hungary).

Treatment. All patients were receiving AM at the moment of being included into the study. After two months, two patients (5%), and after 6 months three more patients (7,5%) were taken off of the drug upon consultation with a cardiologist. In the remaining patients AM could not be discontinued.

Statistical analysis. The incidence rate was calculated using the program Statistica 7.1, StatSoft Inc. Results were expressed as mean ± SD in the text and as the mean ± SEM in the figures. The Rank Order Correlation and the Mann-Whitney's tests were performed. P value ≤ 0,05 was considered significant.

Comparative group. 47 patients with toxic multinodular goiter (TMNG) (39 women and 8 men), matched for age (67 ± 12 yr; range 54–89 yr) and gender, were enrolled in the study as a comparative group. The patients presented normal or elevated RAIU.

RESULTS

The clinical and biochemical data of the AIT and TMNG groups were reported in Tables 1 and 2. The AM dose ranged from 100 to 600 mg/day (mean 204.1 ± 104.2 mg/day). The time of treatment with these drug before radioiodine was 26 ± 22 months. The therapeutic dose of ^{131}I was 800 MBq in patients with AIT, while in comparison group 457.6 ± 251.1MBq. There was no significant difference between mean TSH, free T_3, free T_4 as well as TgAb, TPOAb and TRAb concentrations between those two groups. There was a significant difference in the 5h RAIU between AIT group (2,2 ± 0,6 pmol/l) in comparison to TMNG group (18.0 ± 3.8 pmol/l, $p < 0.001$) and in 24h RAIU, 3.2 ± 0.7 pmol/l) and 35.7 ± 9.1 pmol/l, $p < 0.001$, respectively.

Two months after ^{131}I therapy remission of hyperthyroidism was observed in 8 patients (20%) with AIT, and 21 patients (44,5%) with TMNG.

One year after ^{131}I treatment euthyroidism was achieved in 20 patients (50%) with AIT, and after two years remission of hyperthyroidism was achieved in 38 patients (95%) with AIT. These patients did not require chronic L-thyroxine substitution after radioiodine treatment.

Persistent hypothyroidism was not observed in patients with AIT, but was seen in 32 (68,1%) patients with TMNG two years after ^{131}I treatment.

In t wo-year follow-up recurrence of hyperthyroidism was observed in three (6,4%) patients with TMNG. These patients received a second radioiodine dose 16.2 ± 15 months later. The mean re-treatment dose was 735.93 ± 196.1 MBq.

During follow-up period one patient with AIT required a second ^{131}I dose and another one patient (2.5%) 6 months after ablative ^{131}I dose needed antithyroid medication.

At the same time, transient hypothyroidism was observed in only two patients (5%) with AIT, though was not observed in TMNG.

During follow-up, no sudden deaths in AIT patients were observed, one patient was diagnosed with prostate cancer and in another one patient (woman) amiodanore-induced acute toxic hepatitis was diagnosed.

Table 1. Clinical and biochemical features of the study groups at baseline.

Paremeter	AIT	TMNG	P
No. of patients (F/M)	15/25	39/8	NS
Age (yr)	66.2 ± 5.0	67 ± 12	NS
Family history of hyperthyroidism (%)	12	15	NS
TSH (μU/ml)	0.07 ± 0.06	0.20 ± 0.28	NS
FT4 (pmol/l)	33.5±6.1	25.3 ± 5.8	NS
FT3 (pmol/l)	4.8 ±1.2	4.2±0.2	NS
TPOAb (IU/L)	44.4 ± 17.1	53.2 ± 9.7	NS
TgAb (IU/L)	28.5 ± 15.3	41.2 ± 14.7	NS
TRAb (IU/L)	0.5 ± 0.3	0.4 ± 0.3	NS
5-h RAIU (%)	2.2 ± 0.6	18.0 ± 3.8	$p < 0.001$
24-h RAIU (%)	3.2 ± 0.7	35.7 ± 9.1	$p < 0.001$
Smokers (%)	14	12	NS
Cotinine concentration in urine (ng/mg creatinine)	34.1 ± 10.1	53.1 ± 12.3	NS
Time of treatment with AM before radioiodine (months)	26 ± 22	-	-
Thyroid volume (ml/m^2)	11.1 ± 4.8	34.0 ± 15.8	NS
Administered ^{131}I activity (MBq)	800.0 ± 0.0	457.6 ± 251.1	NS

Data are expressed as mean ± SD. Normal values in our laboratory are as follows: free T_4: 11,5 - 21,5 pmol/L; free T_3: 3,9 – 6,8 pmol/L; TSH: 0,27 - 4,2 μU/mL, TRAb, <2 U/L; TgAb, <60 U/ml; and TPOAb, < 60 U/ml. All patients had undetectable serum TSH, undetectable TgAb, TPOAb, TRAb. Thyroid volume was measured by ultrasonography (normal values range from 18 to 25 ml).
The concentration of cotinine in urine: non smokers (< 5 ng/mg creatinine), passive smokers (from 5 to 50 ng/g creatinine), smokers (> 50 ng/mg creatinine).
NS - not significant

Table 2. Observed effects on hyperthyroidism after 131I administration in studied groups.

Period	Remission *N* (%)		Persistence hypothyroidism *n* (%)		Recurrence hyperthyroidism *n* (%)		Transient hypothyroidism (%)	
	AIT	TMNG	AIT	TMNG	AIT	TMNG	AIT	TMNG
After 2 months	8(20)	21 (44.5)	~	3 (6.5)		4 (8.6)	32 (80)	19 (40.4)
After 6 months	11 (27.5)	8(27)	~	6 (2.8)	1(2.5)	3 (6.4)	28 (70)	30 (63.8)
After 1 year	20 (50)	4 (8.51)	4 (10)	28 (59.6)	~	2 (4.25)	16 (40)	13 (27.7)
After 2 years	38 (95)	12 (25.5)		32(68.1)		3 (6.4)	2(5)	

DISCUSSION

Amiodarone is an iodinated benzofuran derivative that is not only used to treat life-threatening recurrent ventricular arrhythmias (Reiffel *et al.* 1994), but is also used to treat angina, paroxysmal supraventricular tachycardia, atrial fibrillation, and to maintain normal sinus rhythm after cardioversion for atrial fibrillation (Kennedy *et al.* 1994; Podrid 1995). Additionally, its use has been proved to have beneficial effects that can decrease mortality after myocardial infraction (Ceremuzynski *et al.* 1992), although the latter effect has been questioned (Singh *et al.* 1995).

However, it has also severe and frequently occuring side effects, one of which is AIT. Treatment of patients with AIT has always been a challenge. RIT in these patients is considered controversial and may seem to be ineffective, due to low RAIU accompanying this type of hyperthyroidism. However, similarly to the study of Iskandar, in our study, radioiodine was administered despite low RAIU (Iskandar *et al.* 2004). A zero 24h RAIU can be expected in patients exposed to high levels of iodine as present in amiodarone. However, in Europe type 1 AIT is associated with low, normal, or high 24h RAIU, which may be due to an initial borderline low iodine level (Martino *et al.* 1987; Martino *et al.* 2001). Patients with type 2 AIT, exhibit a near zero RAIU. Normal or high radioiodine uptake normally excludes type 2 AIT, however undetectable uptake cannot differentiate between type 1 or 2 AIT. All patients with AIT in our database had a near zero RAIU. In 6 (15%) patients with AIT a transient hypothyroidism was observed for a duration of up to one year. However, after two-year follow-up, it was not observed in any case in the AIT group. In these patients transient L-thyroxine treatment was applied.

Up to now, there has been no clear scientific publication concerning RIT in patients with AIT. Currently available literature lacks data necessary for complete evaluation of radioiodine application in cases with AIT, though Hermida (Hermida *et al.* 2004a; 2004b; 2004c) cites very good results of such treatment. On the other hand, according to Daniels (2001), treatment with radioiodine ablative doses was ineffective when compared to other forms of thyrotoxicosis therapy.

Despite much research having been carried out, pioneered by Bartalena (Bartalena *et al.* 1996), the treatment of AIT still poses a challenge. On the one hand, AM is an effective antiarrhythmic, but on the other hand its application is accompanied by numerous side effects. AIT is difficult to control, and in refractory cases, thyroidectomy has been employed despite the risk it carries in these patients (Farwell *et al.* 1990). In AIT treatment, steroids are a good and effective therapeutic approach, because of their membrane stabilizing and antiinflammatory effects (Bartalena *et al.* 1996). In addition, they are beneficial because of their inhibition of 5'-deiodinase activity. Steroids have been employed in AIH at different doses (15–80 mg prednisone or 3–6 mg dexamethasone daily) and different time schedules (7–12 weeks) (Harjai & Licata 1997; Lombardi *et al.* 1990; Wiersinga 1997). Results of steroid treatment, either alone or in combination with antithyroid drugs or plasmaphoresis, have been favorable in most studies in patients with type II AIT (Bartalena *et al.* 1996; Bonnyns *et al.* 1989; Broussolle *et al.* 1989; Leger *et al.* 1983; Simon *et al.* 1985). Data in type I AIT are scarce, however seem to indicate limited effectiveness (Bartalena *et al.* 1996). Worth mentioning is possible recurrence of thyrotoxicosis when steroid treatment is discontinued (Simon *et al.* 1985; Wimpfheimer *et al.* 1982), which requires reinstitution of treatment in these patients. Chopra (Chopra & Baber 2001) presented five cardiac patients with type II AIT who were treated prospectively with a combination of an oral cholecystographic agent (sodium ipodate, Oragrafin, or sodium iopanoate, Telepaque) and a thionamide (propylthiouracil or methimazole). Iopanoic acid is an iodinated cholecystographic agent that inhibits deiodinase activity and reduces the conversion of T_4 to T_3.

While the mechanism of refractory hyperthyroidism is not known, it is clear that the thyroidal iodine pool is much greater in hyperthyroid patients than in euthyroid patients on AM (Basaria & Cooper 2005). Refractory hyperthyroidism is explained with the larger iodide stores, since antithyroid drugs do not prevent hormone release but at the same time prevent thyroid hormone production. Pharmacological iodide reduces thyroid hormone release from autonomous nodular thyroid glands when new hormone synthesis is inhib-

ited by antithyroid drugs (Basaria & Cooper 2005). A high iodide level persists, even after AM discontinuation, in patients with thyrotoxicosis because of the long half life of amiodarone. Thought the mechanism of action of amiodarone is not fully known and it seems to be senseless to use radioiodine therapy, although in "critical situations" (including in our own experiences) it was a proven treatment and gave very good results.

In our study no differentiation into type I and II AIT was performed, also u*rinary iodine excretion and the newest* differential diagnosis based on ^{99m}Tc-sestaMIBI thyroid scan were not used (Piga *et al.* 2008; Tanda *et al.* 2008). Usefulness of other parameters, such as serum IL-6, C-reactive protein, and thyroglobulin are considered controversial in the differential diagnosis (Bartalena *et al.* 1994; Daniels 2001; Eaton *et al.* 2002; Pearce *et al.* 2003). Before admission to the outpatient clinic, the treating physicians used anti-thyroid medication (carbimazole 20–40 mg daily) and/or corticosteroids (prednisone 30–50 mg/day) according to their clinical discretion (Bartalena *et al.* 1996; 2002; 2004; Bogazzi *et al.* 2001; Reichert & de Rooy 1989).

CONCLUSION

In the study we present a two-year follow-up of patients with AIT treated with radioiodine. RIT turned out to be an effective, safe, and occasionally the only method of treatment in hyperthyroid patients requiring further use of amiodarone, in whom strumectomy and farmocological treatment were contraindicated.

REFERENCES

1 Bartalena L, Brogioni S, Grasso L, Bogazzi F, Burelli A, Martino E (1996). Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge: results from a prospective study. J Clin Endocrinol Metab. **81**: 2930–2933.

2 Bartalena L, Bogazzi F, Martino E (2002). Amiodarone-induced thyrotoxicosis: a difficult diagnostic and therapeutic challenge. Clin Endocrinol (Oxf) **56**: 23–24.

3 Bartalena L, Brogioni S, Grasso L, Rago T, Vitti P & Martino E (1994). Interleukin-6: a marker of thyroid-destructive processes? J Clin Endocrinol Metab. **79**: 1424–1427.

4 Bartalena L, Wiersinga WM, Tanda ML, Bogazzi F, Piantanida E, Lai A, *et al* (2004). Diagnosis and management of amiodarone-induced thyrotoxicosis in Europe: results of an international survey among members of the European Thyroid Association. Clin Endocrinol (Oxf) **61**: 494–502.

5 Basaria S & Cooper DS (2005). Amiodarone and the thyroid. Am J Med. **118**: 706–714.

6 Bogazzi F, Bartalena L, Gasperi M, Braverman LE, Martino E (2001). The various effects of amiodarone on thyroid hormone. Thyroid. **11**: 511–9.

7 Bogazzi F, Miccoli P, Berti P, Cosci C, Brogioni S, Aghini-Lombardi F, *et al* (2002) Preparation with iopanoic acid rapidly controls thyrotoxicosis in patients with amiodarone induced thyrotoxicosis. Surgery. **132**: 1114–1118.

8 Bonnyns M, Sterling I, Renard M, Bernard R, Demaret B, Bourdoux P (1989) Dexamethasone treatment of amiodarone-induced thyrotoxicosis (AIT) with or without persistent administration of the drug. Acta Cardiol **44**: 235–243.

9 Broussolle C, Ducottet X, Martin C, Barbier Y, Bornet H, Noel G, *et al* (1989). Rapid effectiveness of prednisone and thionamides combined therapy in severe amiodarone iodine-induced thyrotoxicosis. Comparison of two groups of patients with apparently normal thyroid glands. J Endocrinol Invest **12**: 37–42.

10 Ceremuzynski L, Kleczar E, Krzeminska-Pakula M, Kuch J, Nartowicz E, Smielak-Korombel J, *et al* (1992). Effect of amiodarone on mortality after myocardial infarction: a double-blind, placebo-controlled, pilot study. J Am Coll Cardiol **20**: 1056–1062.

11 Chopra IJ, Baber K (2001). Use of oral cholecystographic agents in the treatment of amiodarone-induced hyperthyroidism. J Clin Endocrinol Metab. **86**: 4707– 4710.

12 Costagliola S, Morgenthaler NG, Hoermann R, Badenhoop K, Struck J, Freitag D, *et al* (1999). Second generation assay for thyrotropin receptor antibodies has superior diagnostic sensitivity for Graves' disease. J Clin Endocrinol Metab. **84**: 90–97.

13 Daniels GH (2001). Amiodarone-induced thyrotoxicosis. J Clin Endocrinol Metab. **86**: 3–8.

14 Eaton SEM, Euinton HA, Newman CM, Weetman AP & Bennet WM (2002). Clinical experience of amiodarone-induced thyrotoxicosis over a 3-year period: role of colour-flow Doppler sonography. Clin Endocrinol. **56**: 33–38.

15 Farwell AP, Abend SL, Huang SKS, Patwardhan NA, Braverman LE (1990). Thyroidectomy for amiodarone-induced throtoxicosis. J Am Med Assoc. **263**: 1526–1528.

16 Florek E, Piekoszewski W, Wrzosek J (2003). Relationship between the level and time of exposure to tobacco smoke and urine nicotine and cotinine concentration. Pol J Pharmacol. **55**: 97–102.

17 Harjai KJ, Licata AA (1997). Effects of amiodarone on thyroid function. Ann Intern Med. **126**: 64–73.

18 Hermida JS, Jarry G, Tcheng E, Moullart V, Arlot S, Rey JL, *et al* (2004a). Radioiodine ablation of the thyroid to allow the reintroduction of amiodarone treatment in patients with a prior history of amiodarone-induced thyrotoxicosis. Am J Med. Mar. **116**: 345–8.

19 Hermida JS, Jarry G, Tcheng E, Moullart V, Arlot S, Rey JL, *et al* (2004b). Prevention of recurrent amiodarone-induced hyperthyroidism by iodine-131. Arch Mal Coeur Vaiss. **97**: 207–13.

20 Hermida JS, Tcheng E, Jarry G, Moullart V, Arlot S, Rey JL, *et al* (2004c). Radioiodine ablation of the thyroid to prevent recurrence of amiodarone-induced thyrotoxicosis in patients with resistant tachyarrhythmias. Europace. **6**: 169–74.

21 Iskandar SB, Jordan RM, Peris AN (2004). Treating amiodaroneinduced thyrotoxicosis with radioactive iodine. Tenn Med. **97**: 408–10.

22 Kennedy RL, Griffiths H, Gray TA (1989). Amiodarone and the thyroid. Clin Chem. **35**: 1882–1887.

23 Latini R, Tognoni G, Kates RE (1984). Clinical pharmacokinetics of amiodarone. Clin Pharmacokinet. **9**: 136–156.

24 Leger AF, Fragu P, Rougier P, Laurent MF, Tubiana M, Savoie JC (1983). Thyroid iodine content measured by x-ray fluorescence in amiodarone-induced thyrotoxicosis: concise communication. J Nucl Med. **24**: 582–585.

25 Lombardi A, Martino E, Braverman LE (1990). Amiodarone and the thyroid. Thyroid Today. **13**: 1–7.

26 Martino E, Aghjini F, Mariotti S, Bartalena L, Braverman L, Pinchera A (1987). Amiodarone: a common source of iodine-induced thyrotoxicosis. Horm Res. **26**: 158–171.

27 Martino E, Bartalena L, Bogazzi F, Braverman LE (2001). Amiodarone and the thyroid. Endocr Rev **22**: 240–254.

28 Martino E, Safran M, Aghini-Lombardi F, Rajatanavin R, Lenziardi M, Fay M, *et al* (1984). Environmental iodine intake and thyroid dysfunction during chronic amiodarone therapy. Ann Intern Med. **101**: 28–34.

29 McEvoy GK (2000). AHFS drug information 2000. Bethesda, MD: American Society of Health-System Pharmacists.

30 Meurisse M, Hamoir E, D'Silva M, Joris J, Henne G (1993). Amiodarone-induced thyrotoxicosis: is there a place for surgery? World J Surg. **17**: 622–626.

31 Pearce EN, Bogazzi F, Martino E, Brogioni S, Pardini E, Pellegrini G, *et al* (2003). The prevalence of elevated serum C-reactive protein levels in inflammatory and noninflammatory thyroid disease. Thyroid. **13**: 643–648.

32 Piga M, Cocco MC, Serra A, Loy M, Boi F & Mariotti S (2008). The usefulness of 99mTc-sestaMIBI thyroid scan in the differential diagnosis and management of amiodarone-induced thyrotoxicosis. Eur J Endocrinol. **159**: 423–429.
33 Podrid PJ. 1995 Amiodarone: reevaluation of an old drug. Ann Intern Med. **122**: 689–700.
34 Reichert LJ, de Rooy HA (1989). Treatment of amiodarone induced hyperthyroidism with potassium perchlorate and methimazole during amiodarone treatment. Br Med J. **298**: 1547–1548.
35 Reiffel JA, Estes III NA, Waldo AL, Prystowsky EN, Di Bianco R (1994). A consensus report on antiarrhythmic drug use. Clin Cardiol **17**: 103–116.
36 Roti E, Minelli R, Gardini E, Bianconi L, Braverman LE (1993). Thyrotoxicosis followed by hypothyroidism in patients treated with amiodarone: a possible consequence of a destructive process in the thyroid. Arch Intern Med. **153**: 886–892.
37 Simon C, Schlienger JL, Chefran J, Studer H (1985). Efficacitè de la dexamethasone dans le traitement de l'hyperthyroidie à l'amiodarone. Presse Med. **13**: 2767–2770.
38 Singh SN, Fletcher RD, Fisher RG, Singh BN, Lewis HD, Deedwania PC, *et al* (1995). Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmias. Survival trial of antiarrhythmic therapy in congestive heart failure. N Engl J Med. **333**: 77–82.
39 Tanda ML, Bogazzi F, Martino E & Bartalena L (2008). Amiodarone induced thyrotoxicosis: something new to refine the initial diagnosis? Eur J Endocrinol **159**: 359–361.
40 Wiersinga WM (1997). Amiodarone and the thyroid. In: Weetman AP, Grossman A, eds. Pharmacotherapeutics of the thyroid gland. Berlin: Springer Verlag; 225–287.
41 Wimpfheimer C, Staubli M, Schadelin J, Studer H (1982). Prednisone in amiodarone-induced thyrotoxicosis. Br Med J **284**: 1835–1836.