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

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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 glucocorticosteroids.

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 – fT3 and free thyroxine – fT4 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 fT4 level was 18.7 to 38.7 pmol/l (mean: 27.1 ± 5.8) and fT3 concentration was 3.9 to 5.6 pmol/l (mean: 5.7 ± 1.4), while in TMNG patients level of fT4 was 31.5 to 22.2 pmol/l (mean: 25.3 ± 5.8) and fT3 concentration was 3.8 to 4.2 pmol/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
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 radiiodine 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 hyperthyroidism 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 antiarrhythmic 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. 1984). 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 releasing excess iodine, it may favour development of autoimmunological diseases of the thyroid. It causes hyperthyroidism 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, radiiodine 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 assay with 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 ($\pi/6 \times \text{length} \times \text{width} \times \text{depth}$).
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**RAIU and scintigraphy.** RAIU values were measured 5h and then 24h after the administration of a tracer dose (ca. 2MBq of 131I). The thyroid scintiscan was performed 30 min. after i.v. administration of 150 MBq of 99mTc. Images were obtained using Nuclide 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 131I 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 T4 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 131I therapy remission of hyperthyroidism was observed in 8 patients (20%) with AIT, and 21 patients (44,5%) with TMNG.

One year after 131I 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 131I treatment.

In two-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 131I dose and another one patient (2.5%) 6 months after ablative 131I 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) amiodarone-induced acute toxic hepatitis was diagnosed.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AIT</th>
<th>TMNG</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (F/M)</td>
<td>15/25</td>
<td>39/8</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>66.2 ± 5.0</td>
<td>67 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of hyperthyroidism (%)</td>
<td>12</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>TSH (µU/ml)</td>
<td>0.07 ± 0.06</td>
<td>0.20 ± 0.28</td>
<td>NS</td>
</tr>
<tr>
<td>FT4 (pmol/l)</td>
<td>33.5 ± 6.1</td>
<td>25.3 ± 5.8</td>
<td>NS</td>
</tr>
<tr>
<td>FT3 (pmol/l)</td>
<td>4.8 ± 1.2</td>
<td>4.2 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>TPOAb (IU/L)</td>
<td>44.4 ± 17.1</td>
<td>53.2 ± 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>TgAb (IU/L)</td>
<td>28.5 ± 15.3</td>
<td>41.2 ± 14.7</td>
<td>NS</td>
</tr>
<tr>
<td>TRAb (IU/L)</td>
<td>0.5 ± 0.3</td>
<td>0.4 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>5-h RAIU (%)</td>
<td>2.2 ± 0.6</td>
<td>18.0 ± 3.8</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>24-h RAIU (%)</td>
<td>3.2 ± 0.7</td>
<td>35.7 ± 9.1</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>14</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Cotinine concentration in urine (ng/mg creatinine)</td>
<td>34.1 ± 10.1</td>
<td>53.1 ± 12.3</td>
<td>NS</td>
</tr>
<tr>
<td>Time of treatment with AM before radioiodine (months)</td>
<td>26 ± 22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thyroid volume (ml/m2)</td>
<td>11.1 ± 4.8</td>
<td>34.0 ± 15.8</td>
<td>NS</td>
</tr>
<tr>
<td>Administered 131I activity (MBq)</td>
<td>800.0 ± 0.0</td>
<td>457.6 ± 251.1 NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. Normal values in our laboratory are as follows: free T4: 11.5 - 21.5 pmol/L; free T3: 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
**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 infarction (Cermeuzyński et al. 1992), although the latter effect has been questioned (Singh et al. 1995).

However, it has also seen and frequently occurring 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; Bonnaerts 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 T4 to T3.

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-

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

<table>
<thead>
<tr>
<th>Period</th>
<th>Remission N (%)</th>
<th>Persistence hypothyroidism n (%)</th>
<th>Recurrence hyperthyroidism n (%)</th>
<th>Transient hypothyroidism (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIT</td>
<td>TMNG</td>
<td>AIT</td>
<td>TMNG</td>
<td>AIT</td>
</tr>
<tr>
<td>After 2 months</td>
<td>8(20)</td>
<td>21 (44.5)</td>
<td>3 (6.5)</td>
<td>4 (8.6)</td>
</tr>
<tr>
<td>After 6 months</td>
<td>11 (27.5)</td>
<td>8(27)</td>
<td>6 (2.8)</td>
<td>1(2.5)</td>
</tr>
<tr>
<td>After 1 year</td>
<td>20 (50)</td>
<td>4 (8.5)</td>
<td>28 (59.6)</td>
<td>2 (4.25)</td>
</tr>
<tr>
<td>After 2 years</td>
<td>38 (95)</td>
<td>12 (25.5)</td>
<td>32(68.1)</td>
<td>3 (6.4)</td>
</tr>
</tbody>
</table>
ilited 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 urinary iodine excretion and the newest differential diagnosis based on 99mTc-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 farmacological treatment were contraindicated.

REFERENCES


