Long-term outcome of thyroid function after amiodarone-induced thyrotoxicosis, as compared to subacute thyroiditis

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ABSTRACT. Background: Two main forms of amiodarone-induced thyrotoxicosis (AIT) exist: type 1 AIT is a condition of true hyperthyroidism developing in patients with pre-existing thyroid disorders, and usually requires thyroid ablative treatment. On the other hand, type 2 AIT is a form of destructive thyroiditis occurring in normal thyroids, the management of which usually consists in glucocorticoid treatment. Aim: To assess the long-term outcome of thyroid function in a prospective study of type 2 AIT patients, as compared to patients with De Quervain’s subacute thyroiditis (SAT). Patients and Methods: Sixty consecutive patients with type 2 AIT were evaluated during oral glucocorticoid treatment (oral prednisone 30 mg/day, gradually tapered and withdrawn over a 3-month period) and followed for 38±4 months (range 6-72) thereafter. Sixty consecutive patients with SAT, referred to our Institutes during the same period and treated with the same therapeutic schedule, served as controls. Results: Type 2 AIT patients were older (p<0.0001) and showed a larger male preponderance (M:F 3.6:1 vs 0.5:1, p<0.0001) than SAT patients. Mean serum free T₄ (FT₄) and free T₃ (FT₃) concentrations at diagnosis were increased in both conditions, but higher in type 2 AIT than in SAT (FT₄ 47.6±18.8 and 29.6±8.3 pmol/l, respectively, p<0.0001; FT₃ 15.4±7.0 and 11.2±3.0 pmol/l, respectively, p<0.001). Correction of thyrotoxicosis was obtained in all patients in both groups, but restoration of euthyroidism occurred earlier in SAT than in type 2 AIT (p=0.006). Ten type 2 AIT patients (17%) and 3 SAT patients (5%, p<0.03) became permanently hypothyroid after glucocorticoid withdrawal and required levothyroxine replacement. Conclusions: A relevant proportion of type 2 AIT patients develop permanent hypothyroidism after correction of thyrotoxicosis. Thus, periodic surveillance of thyroid status is required after type 2 AIT.

INTRODUCTION

Amiodarone is an iodine-rich drug widely used and very effective in the management of tachyarrhythmias and, to a lesser extent, severe heart failure (1, 2). The drug causes changes in thyroid function tests, namely an increase in serum T₄ and a relative decrease in serum T₃ even in euthyroid subjects, mostly due to inhibition of T₄ peripheral monodeiodination (1-4). Overt thyroid dysfunction, either hypothyroidism or thyrotoxicosis, occurs in about 15% of subjects under chronic amiodarone therapy (1-5). Amiodarone-induced hypothyroidism is relatively more frequent in iodine-sufficient areas, amiodarone-induced thyrotoxicosis (AIT) in iodine-deficient areas (6). Treatment of AIT is a difficult challenge (7-9). Two main forms of AIT exist: type 1 occurs in patients with pre-existing thyroid disorders (usually autonomous nodular goiter or subclinical Graves’ disease) and is a true form of iodine-induced hyperthyroidism. At variance, type 2 AIT is a form of drug-induced destructive thyroiditis apparently occurring in the absence of intrinsic thyroid gland abnormalities. Differentiation of the two main forms can often be made by conventional thyroid ultrasonography,

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color flow Doppler sonography (CFDS), thyroidal radioactive iodine uptake (RAIU), serum interleukin-6 levels, presence/absence of circulating thyroid autoantibodies (10-12). However, mixed (or indefinite) forms, in which both pathogenic mechanisms (thyroid hormone hypersecretion and destructive processes) intervene, are likely more frequent than previously believed (1, 9). While type 1 AIT and mixed forms are usually initially treated with a combination of thionamides and potassium perchlorate (and, in many instances, glucocorticoids), type 2 AIT is generally and effectively managed by glucocorticoids alone (1, 9). Because type 1 AIT occurs in an abnormal thyroid gland, thyroid ablation by either thyroidectomy or radioactive iodine (after removal of iodine contamination) is often required after correction of thyrotoxicosis (1, 9).

On the other hand, further treatments are rarely needed in type 2 AIT due to the absence of intrinsic abnormalities of the thyroid gland in this condition (1, 9). However, the long-term outcome of thyroid function and, in particular, the possible late consequences of thyroid damage after type 2 AIT, are largely unknown. The aim of the present study was to assess the long-term outcome of thyroid function in a large series of prospectively followed type 2 AIT patients.

**MATERIALS AND METHODS**

**Subjects**

The study included 60 consecutive, untreated patients with type 2 AIT (47 men, 13 women, mean (+SD) age 67±13 yr; range 33-84 yr) seen at the Department of Endocrinology, University of Pisa and Department of Clinical Medicine, University of Insubria at Varese from 1998 to 2004. The first 60 consecutive patients with subacute thyroiditis (SAT) (19 men, 41 women, age 49±11 yr; range 30-76 yr) referred to our departments during the same period served as controls. During the same period, 33 patients with type 1/mixed forms of AIT were observed.

Diagnosis of AIT was based on clinical and laboratory features, including increased free T₄ (FT₄) and free T₃ (FT₃) concentrations and undetectable serum TSH levels in patients chronically treated with amiodarone. Duration of amiodarone therapy ranged from 2-148 months (mean±SD, 26±24) and the cumulative dose of amiodarone ranged from 9-434 g (mean±SD, 113±83). Diagnosis of type 2 AIT was based on the following criteria: normal thyroid gland at conventional ultrasonography, absent hypervascularity at CFDS, absence of circulating thyroid autoantibodies [anti-thyroglobulin (Tg), anti-thyroid peroxidase (TPO), anti-TSH receptor (TRAb)], and low (≤3%)/undetectable RAIU values.

Diagnosis of SAT was made according to clinical and biochemical findings, including anterior neck pain with or without systemic symptoms, low-grade fever, sore throat or upper respiratory tract infection, elevated erythrocyte sedimentation rate, increased serum FT₄ and FT₃ levels and undetectable TSH concentrations, absent vascularity at CFDS, and low/undetectable thyroidal RAIU values.

**Conventional and color flow Doppler sonography**

Thyroid volume was measured by ultrasound and calculated by the ellipsoid model (width x length x thickness x 0.52 for each lobe) as previously described (13). CFDS was performed as previously reported (14).

**Assays**

Serum FT₄, FT₃ (Technogenetics, Milan, Italy), TSH (Delphia, hTSH ultra kit; Pharmacia, Turku, Finland), TRAbs (TRAK assay, Henning, Berlin, Germany), anti-Tg (Serodia, Tokio, Japan) anti-TPO (Sorin Biomedica, Saluggia, Italy) were measured by commercial kits. Normal values in our laboratory are as follows: FT₄, 8.3-21.2 pmol/l; FT₃, 3.8-8.4 pmol/l; TSH, 0.4-3.7 mU/l; anti-Tg and anti-TPO, negative; TRAb, <1U/l.

**Thyroidal RAIU**

Thyroidal RAIU values were measured 3 and 24 h after the administration of a tracer dose (5 μCi) of 131-I. Normal 3-h and 24-h RAIU values in our area are 10-20 and 30-45%, respectively.

**Urinary iodine excretion**

Morning random urinary samples were collected for iodine measurements using an autoanalyzer apparatus (Technicon, Rome, Italy). The median urinary iodine excretion in our area is 110 μg/l.

**Treatment**

Amiodarone treatment was withdrawn in all patients. All patients were treated with oral prednisone (starting dose, 30 mg/day). The drug was gradually tapered and withdrawn after three months. Cure of thyrotoxicosis was defined by normalization of both serum FT₄ and FT₃, as previously reported (15). Hypothyroidism was considered permanent when serum TSH concentrations remained higher than normal (with a concomitant decrease in serum free thyroid hormone concentrations in 3 subsequent determinations after at least 6 months from glucocorticoid withdrawal). Mean follow-up period was 38±4 months (range 6-72 months) in type 2 AIT and 40±5 months (range 9-76 months) in SAT.

**Statistical analysis**

Results were expressed as mean±SD. Comparison of FT₄, FT₃, RAIU and thyroid volume between the study groups was performed by the analysis of variance (ANOVA); differences in the occurrence of hypothyroidism in the two groups was evaluated by chi-square and the Fisher's exact test.

**RESULTS**

Clinical and biochemical features of the study groups at baseline are shown in Table 1. Patients with type 2 AIT were older than those with SAT (p<0.001), with prevalence of male gender (M:F 3.6:1); at variance, most patients with SAT were women (M:F 0.5:1, p<0.0001; Table 1).

Mean serum FT₄ and FT₃ concentrations at diagnosis were increased in both groups, but higher in type 2 AIT than in SAT (FT₄, 47.6±18.8 and 29.6±8.3 pmol/l, respectively, p<0.0001; FT₃ 15.4±7.0 and 11.2±3.0