Twenty-Four Hour Radioactive Iodine Uptake in 35 Patients with Amiodarone Associated Thyrotoxicosis

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Amiodarone associated thyrotoxicosis (AAT) occurs in ~10% of patients treated with this iodine rich drug in areas of mild iodine deficiency. The thyroid radioactive iodine uptake (RAIU) is usually undetectable or very low in iodine-induced thyrotoxicosis. In the present study, 35 patients with AAT were evaluated. Twelve patients had no thyroid abnormalities by physical exam and all had 24-hr RAIU ≤ 4%. In contrast, nine of 11 patients with AAT and diffuse goiters and eight of 12 patients with AAT and nodular goiters had RAIU values greater than 8%. In patients with AAT and goiter it appears possible that the thyroid fails to adapt normally to the excess iodide load, resulting in an inappropriately high RAIU in the presence of excess plasma iodine.

J Nucl Med 26: 1402–1407, 1985

Iodine-induced thyrotoxicosis has been recognized for many years in iodine deficient areas since the introduction of iodine prophylaxis for goiter (Jod-Basedow disease) (*1*). Hyperthyroidism occurring after acute and chronic administration of iodine-containing drugs has also been observed in patients with or without underlying thyroid abnormalities residing in both iodine deficient and sufficient areas (*1–5*). Recently, amiodarone, an iodine rich drug containing 37.5 mg iodine per 100 mg and widely used for the treatment of tachyarrhythmias and ischemic heart disease, has been associated with a relatively high incidence (~10%) of iodine-induced thyrotoxicosis in continental Western Europe where environmental iodine intake is marginally low (*5*).

In iodine-induced thyrotoxicosis, the thyroid radioactive iodine uptake (RAIU) is usually undetectable or very low (*1*), although occasionally the RAIU has been reported to be normal or rarely elevated (*6–9*). In the present study, the RAIU was assessed in a large number of patients with amiodarone associated thyrotoxicosis (AAT).

Received Mar. 18, 1984; revision accepted Aug. 2, 1985.

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MATERIAL AND METHODS

Patients

Thirty-five consecutive patients (15 M, 20 F) aged 32–71 yr (mean 57 yr) with AAT were studied. All patients resided in West Tuscany, Italy, an area of moderate iodine deficiency. The drug was administered chronically (4–18 mo) at a dose of 100–250 mg daily. Clinical evidence of thyrotoxicosis developed during amiodarone administration in 22 patients and 1 to 4 mo after withdrawal of the drug in 13 patients. The patients were divided into three groups according to the presence of diffuse goiter (Group A), nodular goiter (Group B), or absence of goiter (Group C). Thyroid gland abnormalities were established on the basis of physical examination, thyroid ultrasound and, when feasible, thyroid scintigraphy. Group A consisted of 11 patients with diffuse goiter (5 M, 6 F) age 41–67 yr (mean 55 yr) and Group B, 12 patients (2 M, 10 F) age 52–77 yr (mean 64 yr). In Group B, seven patients had multinodular goiter and five patients a solitary adenoma. Mild Graves' ophthalmopathy was present in only one patient in Group A. Group C consisted of 12 patients (8 M, 4 F) age 32–68 yr (mean 53 yr), none of whom had a goiter.

Laboratory tests

Thyroid function tests in serum were carried out as follows: serum total thyroxine (T_4) and total triiodothy-

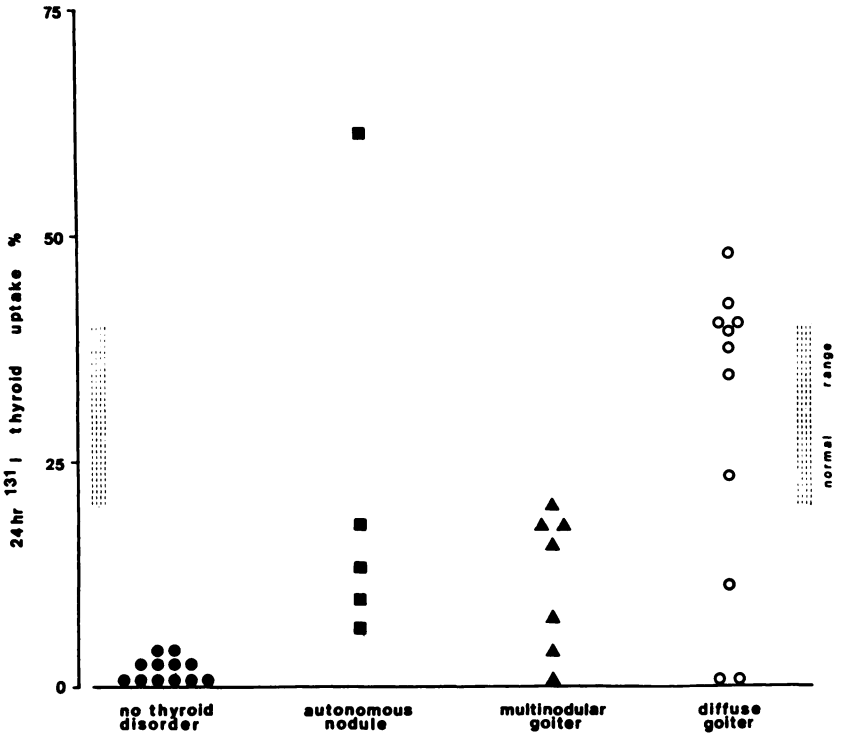

FIGURE 1
24-hr thyroid RAIU (% dose) in all patients with AAT

ronine (T_3), T_4-RIA and T_3-RIA kits ARIA II,* T_3 resin uptake (RT_3U), Trilute kit,† free T_4 index (FT_4I) and free T_3 index (FT_3I) were calculated as the product of the T_4 or T_3 and the RT_3U, respectively; free T_4 (FT_4) and free T_3 (FT_3), Lysophase T_4 and Lysophase T_3 kits,‡ according to the method of Romelli et al. (*10*); serum thyrotropin (TSH),§ antithyroglobulin (anti-T_g) and antimicrosomal (anti-M) antibodies by tanned red cell hemagglutination.¶ The thyroid RAIU was determined 24 hr after the administration of 50 μCi of iodine-131 (^{131}I). The thyroid gland was examined in all patients by ultrasound and, when feasible, by ^{131}I scintigraphy. The urinary iodine in a spot urine was measured by the modified method of Zak (*11*) and the results expressed as μg iodine per g creatinine. Urinary iodine excretion was available in 80% of the patients on or off amiodarone at the time of diagnosis of thyrotoxicosis.

Diagnosis of amiodarone iodine induced thyrotoxicosis

Since serum T_4, FT_4I and FT_4 concentrations may be elevated in euthyroid patients chronically treated with amiodarone (*5*, *12–15*), the diagnosis of AAT was made on the basis of elevated serum T_3, FT_3I and FT_3 concentrations, undetectable serum TSH concentrations (all patients), no TSH response to i.v. thyrotropin releasing hormone (TRH) administration (all patients), and the presence of clinical evidence of hyperthyroidism including weight loss, sweating, nervousness, tremor, diarrhea and increasing heart rate despite amiodarone administration (*5*). While previous biochemical evidence of euthyroidism was available in only 30% of the patients, all patients were clinically euthyroid at the time amiodarone therapy was begun.

Statistics

Statistical analysis was performed using an analysis of variance (ANOVA) followed by Student-Neuman-Keuls test for multiple comparisons where necessary.

RESULTS

The clinical and biochemical data of the patients with AAT are reported in Table 1. The serum concentrations of total and free thyroid hormones were elevated and similar in all three groups. The serum concentration of TSH was undetectable in all patients with AAT. The TSH response to TRH was absent in all patients. Circulating anti-Tg and/or anti-M antibodies were present in the majority of patients (73%) with toxic diffuse goiter and in one patient with toxic multinodular goiter. They were undetectable in all patients with a solitary toxic adenoma and in patients without goiter. Urinary iodine excretion was measured in 21 patients, including those who were no longer taking amiodarone, and was elevated in all, with values ranging between 700 and 5,000 μg iodine per g creatinine. These values were markedly elevated as compared to those observed in normal subjects residing in the same area who were not receiving amiodarone or any other iodine-containing drug (77.8 $\pm$ 3.7 μg iodine/g creatinine, mean $\pm$ s.e.e.).

The 24-hr thyroid RAIU values are shown in Fig. 1.

TABLE 1

Patient no.	Sex/age	Receiving amiodarone at time of DX	T_4 (μg/dl)	FT4I	T_3 (ng/dl)	FT3I	FT4 (pg/ml)	FT3 (pg/ml)	Anti-Tg	Anti-M	24-hr RAIU (% dose)	Thyroid examination
Group A												
1	M 57	4*	20.0	27.5	349	437	—	—	neg	1:400	35	Diffuse goiter
2	M 55	Yes	13.5	18.8	271	380	48.0	13.6	neg	1:102,400	1	Diffuse goiter
3	F 62	4*	17.1	23.1	325	440	47.3	14.0	neg	1:6,400	36	Diffuse goiter
4	F 54	Yes	21.6	26.3	302	382	67.5	30.5	neg	1:25,600	32	Diffuse goiter
5	M 47	Yes	17.6	25.0	466	662	36.0	16.0	1:100	1:6,400	33	Diffuse goiter
6	F 58	4*	18.0	27.5	450	450	115.0	38.3	neg	neg	10	Diffuse goiter
7	M 54	Yes	13.8	16.0	280	325	—	—	neg	neg	36	Diffuse goiter
8	F 41	Yes	20.0	28.5	225	398	54.0	21.0	1:40	neg	1	Diffuse goiter
9	F 67	1*	19.0	18.4	377	354	—	—	neg	neg	31	Diffuse goiter
10	M 58	Yes	14.0	17.1	320	388	—	—	1:80	1:25,600	46	Diffuse goiter
11	F 48	Yes	19.0	25.3	420	559	52.0	16.0	neg	1:25,600	24	Diffuse goiter
		Mean ± s.e.e.	17.6 ± 0.8	23.0 ± 1.4	344 ± 23	434 ± 29	60.0 ± 9.8	21.3 ± 3.6			26 ± 5	
Group B												
12	F 77	Yes	17.5	26.6	265	403	36.0	14.0	neg	neg	5	Multinodular goiter
13	F 67	Yes	13.0	14.9	295	340	—	—	neg	neg	7	Multinodular goiter
14	F 76	3*	17.3	23.0	297	394	48.0	13.8	neg	neg	15	Multinodular goiter
15	F 75	Yes	12.4	16.2	290	379	—	—	neg	neg	19	Multinodular goiter
16	M 55	Yes	18.4	26.4	390	461	—	—	1:40	1:1,600	16	Multinodular goiter
17	F 67	4*	20.0	30.2	287	433	46.9	29.0	neg	neg	1	Multinodular goiter
18	F 55	Yes	16.1	16.9	254	274	—	—	neg	neg	16	Multinodular goiter
19	F 56	Yes	13.6	17.1	329	416	29.0	16.0	neg	neg	9	Single hot nodule
20	F 52	Yes	10.3	13.7	314	418	38.1	21.0	neg	neg	16	Single hot nodule
21	F 70	Yes	12.0	13.8	340	392	—	—	neg	neg	64	Single hot nodule
22	M 58	Yes	20.1	21.7	358	425	37.9	28.9	neg	neg	6	Single hot nodule
23	F 55	3*	20.0	43.0	321	691	47.1	31.0	neg	neg	13	Single hot nodule
		Mean ± s.e.e.	15.9 ± 1.0	22.0 ± 2.5	312 ± 11	419 ± 28	40.4 ± 2.7	22.0 ± 2.9			16 ± 5	
Group C												
24	M 60	2*	25.4	36.2	306	429	60.0	19.0	neg	neg	2	Normal
25	M 32	Yes	13.1	17.7	356	485	48.0	19.0	neg	neg	3	Normal
26	M 46	Yes	25.2	29.7	346	401	47.0	27.0	neg	neg	1	Normal
27	F 39	Yes	21.3	26.1	259	318	63.7	19.0	neg	neg	2	Normal
28	M 67	2*	16.0	20.5	330	424	60.0	25.3	neg	neg	2	Normal
29	F 68	Yes	11.0	14.9	440	450	34.2	22.1	neg	neg	4	Normal
30	M 51	3*	10.0	18.1	218	248	—	—	neg	neg	1	Normal
31	F 59	1*	14.3	21.7	292	428	41.0	17.1	neg	neg	4	Normal
32	M 55	2*	17.4	25.1	345	432	—	—	neg	neg	1	Normal
33	M 59	Yes	14.7	19.4	251	332	32.0	12.1	neg	neg	2	Normal
34	F 50	Yes	12.6	12.0	234	223	22.7	8.2	neg	neg	1	Normal
35	M 69	1*	16.3	23.0	320	450	—	—	neg	neg	1	Normal
		Mean ± s.e.e.	16.4 ± 1.5	22.0 ± 1.9	308 ± 18	385 ± 24	45.4 ± 4.7	18.8 ± 2.0			2 ± 0.3†	
Normal range			4.2–12.0	4–11	100–210	100–208	6–16	2.5–5.0			24–47	

*Number of months off amiodarone at time of diagnosis of thyrotoxicosis.
†$p = 0.0005$ vs. Groups A and B.
Serum TSH was < 0.5 μU/ml in all patients.

The RAIU was very low (≤4%) in all 12 patients without goiter (Group C). In contrast, the RAIU was within the normal range (24–47%) in eight of the 11 patients with diffuse goiter (Group A) (34 ± 2%; range 24–46%) and was 10% or lower in the other three. In the patients with AAT and nodular goiter (Group B), the RAIU was elevated in one (64%), was completely suppressed in one (1%) and ranged between 5 and 19% in the remaining 12 patients (12 ± 2%). There was no difference in the RAIU in patients from Group A compared with those from Group B.

There was no relationship between the RAIU and whether the patient was studied during amiodarone therapy or 1 to 4 mo after the drug was discontinued for all

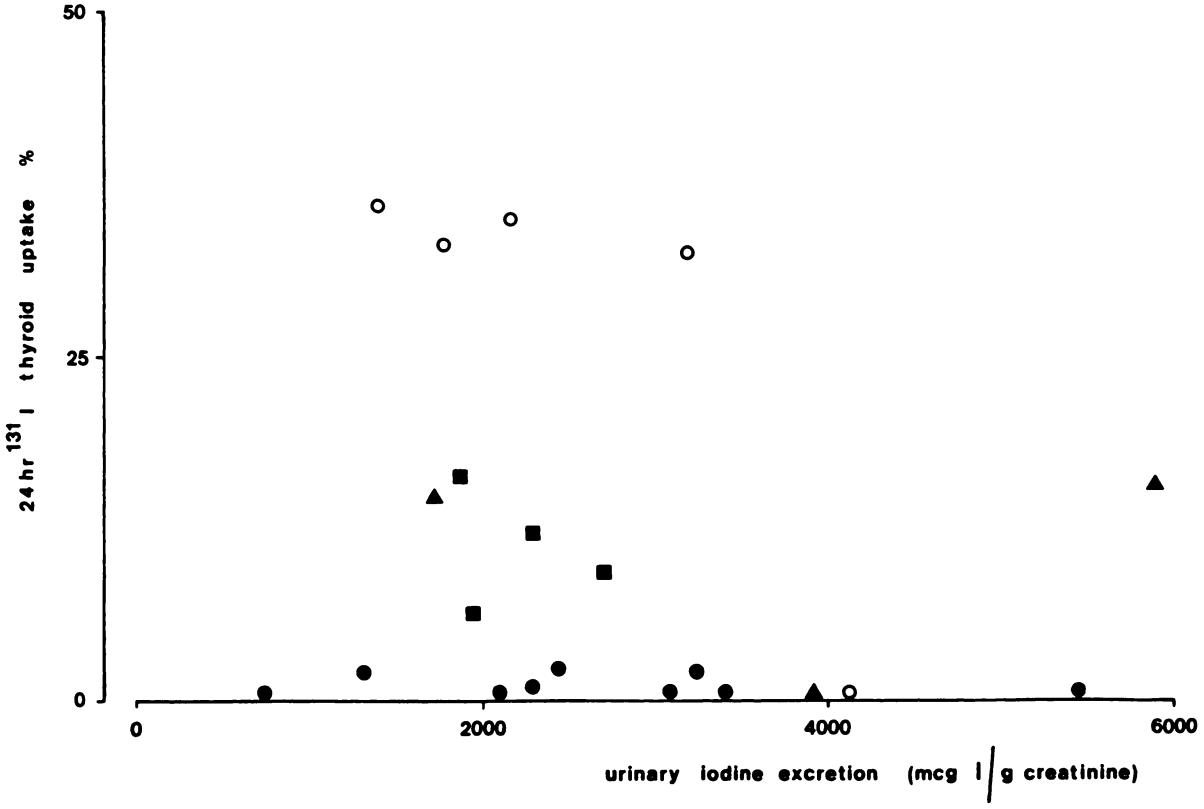

FIGURE 2
Relationship of 24-hr thyroid RAIU (% dose) to urinary iodine excretion (μg iodine/g creatinine): (●) Normal thyroid; (■) Single hot nodule; (▲) Multinodular goiter; (○) Diffuse goiter

patients or for patients in each group. The mean RAIU values in patients with diffuse toxic goiter or nodular toxic goiter who had not received iodine containing drugs were 70 ± 4% (n=45) and 53 ± 2% (n=45), respectively. The RAIU was less than 4% in 14 euthyroid patients chronically treated with amiodarone, four of whom had diffuse goiter. Figure 2 illustrates the relationship between the thyroid RAIU and urinary iodine excretion in the AAT patients. There was no significant correlation between these two parameters in any of the diagnostic groups. In addition, there was no correlation between the RAIU and the serum T_4 or T_3 concentrations.

DISCUSSION

Amiodarone is a potent inhibitor of the outer ring or 5'-deiodination of T_4 and rT_3, resulting in an increase in serum T_4 and RT_3 concentrations and a decrease in the serum T_3 concentration in euthyroid subjects (*12–16*). In addition, there is a high incidence of amiodarone associated thyroid dysfunction. A high incidence of hyperthyroidism secondary to amiodarone therapy has been reported in areas of relative iodine deficiency (*3,4,17*), while hypothyroidism is a more common occurrence in areas of iodine sufficiency (*5,17–19*). Iodine-induced thyrotoxicosis secondary to other iodine rich medications or x-ray contrast agents may also occur in patients with or without goiter (*1,2,5*). These observations suggest that the presence of goiter is not a necessary prerequisite for the development of thyrotoxicosis following iodine administration.

The mechanism by which amiodarone and other iodine containing drugs induce thyrotoxicosis is unclear. We have recently reported that amiodarone therapy does not induce thyroid autoimmunity (*20*). However, it appears likely that underlying thyroid autoimmunity may be a risk factor for the development of amiodarone iodine-induced thyroid dysfunction since thyroid autoantibodies are present in many patients who develop hypothyroidism (*5, 17*) and thyrotropin receptor antibodies are observed in some patients who develop hyperthyroidism (*20*). In the present study, thyroid autoantibodies were detectable in 73% of patients with toxic diffuse goiter and were absent in 11 of 12 patients with multinodular or uninodular goiter and in all 12 patients without goiter.

It is generally accepted that the 24-hr thyroid RAIU is very low or undetectable in patients with iodine-induced thyrotoxicosis. However, normal or elevated RAIU values have been reported in an occasional patient. Thus, Fairhurst and Neguin (*8*) reported an RAIU value of 52% in one patient with multinodular goiter who developed thyrotoxicosis after cholecystography. Nilsson (*7*),

Delzant and Massin (*21*), and Benhoit et al. (*9*) have also reported a few patients with iodine-induced thyrotoxicosis and an inappropriate elevation in the thyroid RAIU. The results in the present series of 35 patients with AAT indicate that the thyroid RAIU is detectable and relatively high with respect to the large amount of iodine intake in the majority of patients with goiter; 17 of 23 patients (74%) with nodular or diffuse goiter had RAIU values above 8%. In contrast to the patients with goiter, the RAIU was less than 4% in all 12 patients who had no evidence of goiter or underlying thyroid disease. The mean RAIU in the AAT patients with toxic nodular goiter was lower than that observed in AAT patients with diffuse toxic goiter (16 ± 5% compared with 26 ± 5%) but this difference was not significant due to the large range observed in both groups. Lower RAIU values in patients with toxic nodular goiter as compared to those with diffuse toxic goiter are also seen in patients with noniodine-induced thyrotoxicosis. There was no difference in serum total or free thyroid hormone concentrations between patients with and those without goiter or between patients with suppressed or nonsuppressed thyroid RAIU. In addition, the RAIU was not related to the quantity of iodine intake as assessed by determination of urinary iodine excretion.

The thyroid RAIU was almost always undetectable in euthyroid amiodarone treated patients irrespective of the presence or absence of goiter. This is consistent with the observations of Léger et al. (*22*) who reported elevated thyroid iodine content measured by an iodine fluorescence technique in patients with amiodarone associated thyrotoxicosis but normal values in euthyroid patients treated with amiodarone. It seems possible, therefore, that in patients with AAT the thyroid fails to adapt to excess plasma iodide by decreasing the active transport of iodide from the plasma into the thyroid, resulting in an increased intrathyroid iodine content. This could permit excess thyroid hormone synthesis and release by a mechanism which remains poorly understood. The phenomenon of iodine-induced thyrotoxicosis is far more common in areas of endemic iodine deficiency suggesting that the iodine-deficient thyroid is more susceptible to hyperthyroidism induced by increased intrathyroid iodine.

It has been reported that thyrotoxicosis may spontaneously remit in patients with AAT (*2, 3, 23*). We have recently observed that this spontaneous remission occurs more frequently in patients without evidence of underlying thyroid abnormalities than in those with diffuse or nodular goiters (*23*). In the present study, an elevated thyroid RAIU was far more common in patients with diffuse or nodular goiters than in patients without underlying thyroid disease. This raises the possibility that the more protracted thyrotoxicosis observed in the patients with goiter is due to a greater intrathyroid iodine content secondary to the higher thyroid uptake of iodine. Unfortunately, we were unable to measure intrathyroid iodine content by fluorescence techniques in the thyrotoxic patients with and without an elevated thyroid RAIU to evaluate this possibility.

ACKNOWLEDGMENT

This work was supported by grant of CNR, Rome, Italy, by Grant AM 18919 from the NIAMDD, NIH, Bethesda, MD, and the John and Ethel Goldberg Research Fund.

FOOTNOTES

*Beckton-Dickinson Laboratory System, Milan, Italy.
†Miles Italiana S.p.A. Ames Division, Milan, Italy.
‡Dow-Lepetit S.p.A., Milan, Italy.
§Byk-Mallinckrodt S.p.A., Milan, Italy.
¶Fujizoki Pharmaceutical Co., Tokyo, Japan.

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