Clinical Characteristics of Amiodarone-Induced Thyrotoxicosis and Hypothyroidism in Japan

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Abstract. Since amiodarone was introduced in Japan in 1992, the incidence of the drug-induced thyroid dysfunction has been increasing. We studied the thyroid function of 13 patients with amiodarone-induced thyrotoxicosis (AIT) and 11 patients with amiodarone-associated hypothyroidism (AAH) who had been referred to our Institute in the last 6 years. AIT and AAH developed after 39 ± 21 and 20 ± 16 months of amiodarone treatment, respectively. One patient developed AAH followed by AIT. The AIT ranged from subclinical to overt thyrotoxicosis. Four patients with moderate to marked AIT were treated with methimazole. Their thyrotoxicosis persisted for 3 to 9 months, despite administration of antithyroid agents. One patient with mild thyrotoxicosis was treated with prednisolone, resulting in a euthyroid state in a few months. Eight patients with asymptomatic to moderate thyrotoxicosis resolved spontaneously without any treatment. In four asymptomatic patients with AIT, serum levels of T_3 and T_4 were in the upper normal range or slightly high ($< 12 \mu\text{g/dl}$), accompanied by suppressed TSH ($< 0.1 \mu\text{U/ml}$) and high thyroglobulin levels, suggesting destruction-induced thyrotoxicosis. Such a subclinical thyrotoxicosis developed repeatedly in one patient. Ultrasonographic studies revealed no nodular lesion in the thyroid, and color flow Doppler sonography demonstrated no hypervascularity in the thyroid gland in any AIT patient. Although it is postulated in Europe that there are two types of AIT, namely type I, which develops in patients with latent Graves' disease or toxic multinodular goiter, and type II, which develops in an apparently normal thyroid as destructive thyroiditis, all AIT patients we have seen so far had developed destructive type AIT. Sufficient intake of iodide and a very low incidence of toxic multinodular goiter may account for the rare incidence of type I AIT in our country. Mild to moderate AIT resolved spontaneously without discontinuing amiodarone, but it was discontinued in two of 13 AIT patients because of extrathyroidal adverse reactions.

Key words: Amiodarone, Thyrotoxicosis, Hypothyroidism, Color flow Doppler sonography, Iodide

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AMIODARONE, an effective type III anti-arrhythmic drug, contains a high amount of iodine (37%). Since approximately 10% of organic iodine is deiodinated to yield free iodine, it elicits adverse effects

on thyroid function [1, 2]. Furthermore, amiodarone has directly cytotoxic effects on human and rodent thyrocytes *in vitro* [3, 4]. It is therefore well known that the agent elicits various adverse effects on thyroid function, leading to either hypothyroidism or hyperthyroidism [5–7].

In general, amiodarone-associated hypothyroidism (AAH) elicits no significant problem clinically: simple supplementation with L-thyroxine without discontinuing amiodarone is suffice to keep the AAH patients euthyroid. In contrast, amiodarone-in-

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duced thyrotoxicosis (AIT) is difficult to treat, because a lot of iodine accumulated in the thyroid gland, and withdrawal of the agent is not efficient because of its extremely protracted half life of 14–53 days [2]. Furthermore, it is not recommended for patients with life-threatening arrhythmia to discontinue the life-sustaining antiarrhythmic. Although mild to moderate AIT may spontaneously resolve, it may be fatal in some protracted cases [8, 9, 10], indicating that early diagnosis and proper management is mandatory for AIT patients.

AIT is considered to be less frequent in patients living in iodine-sufficient areas [11], but an increasing number of patients with AIT have been reported in Japan [12, 13], where iodine intake is still sufficient [14]. In our country, amiodarone was first marketed in October 1992, and more than 200 patients, who had been unresponsive to conventional antiarrhythmic agents, were prescribed amiodarone at the Heart Institute of Japan in Tokyo Women's Medical University. For the last 6 years, 13 patients with AIT and 11 with AAH have been referred to the Institute of Clinical Endocrinology for evaluation of thyroid dysfunction. We found that thyrotoxicosis of AIT patients ranged widely from subclinical to overt and that the pathogenesis of AIT is very different from that reported in Europe, where iodine intake is moderately deficient.

Subjects and Methods

Between 1992 and October 1998, 23 patients with amiodarone-induced thyroid dysfunction were referred to the Institute of Clinical Endocrinology. Thirteen patients developed AIT and eleven AAH. One patient first developed AAH, followed by AIT. When serum levels of T_4 , free T_4 , T_3 or free T_3 were above the normal range, and /or TSH became undetectable ($<0.1 \mu\text{U/ml}$), at least twice consecutively, at an interval of more than two months, the patients were considered to have developed AIT. When the serum levels of thyroid hormones were decreased or in the lower normal range, and serum levels of TSH were increased to more than $10 \mu\text{U/ml}$ after several months of amiodarone therapy [1], or increased steadily with progressively decreasing serum levels of T_3 and T_4 , the patients were considered to have developed AAH. At the first visit, informed

consent was obtained and 20 ml of blood was taken for measurement of thyroid hormones, thyroglobulin and TSH receptor antibody (TRAb). Urine was collected for measurement of iodide. Serum levels of T_3 (normal range; 90–170 ng/dl) and T_4 (normal range; 5.1–11.4 $\mu\text{g/dl}$) were determined with commercial radioimmunoassay kits. Serum levels of free T_3 (normal range; 2.5–5.0 pg/ml) and free T_4 (normal range; 0.95–1.85 ng/dl) were determined using chemiluminescence assay kits. The serum level of TSH (normal range; 0.2–4.0 $\mu\text{U/ml}$) was determined with immunoradiometric assay kits. Antithyroid microsomal antibody and antithyroglobulin antibody were determined with commercially available kits (Fuji Rebio, Tokyo, Japan). A reciprocal titer of 1 : 100 or more was considered positive. TRAb was determined by a radioreceptor assay with a commercial kit (Baxter Co., Tokyo). The results were expressed as percentage inhibition of the binding of ^{125}I -bTSH. The normal range was between –10% to 10%.

The inorganic iodide concentration in urine was determined with a spectrophotometer (Teijin Biochemical Laboratory, Tokyo, Japan) [14], and the data were expressed as mg iodine/g creatinine.

Color flow Doppler sonography was performed with a 7.5 MHz transducer (Model LOGIQ500, GE Yokogawa Medical System Co., Tokyo, Japan). Qualitative color flow Doppler sonographic signals were classified as follows [16, 17]: pattern 0: absent intraparenchymal vascularity or minimal spots, pattern I: presence of parenchymal blood flow with patchy uneven distribution or intranodular spots; pattern II: mild increase in color flow Doppler signal with patchy distribution, or prominent color flow at the periphery of the nodule; pattern III: markedly increased color flow Doppler signals with diffuse homogenous distribution or marked color flow throughout the entire nodule, including the so called "thyroid inferno" (Fig. 1).

Results

Thyroid function of patients with AIT and AAH

Thyroid function of patients with AIT and AAH is shown in Tables 1 and 2, respectively. Consistent with previous reports, the serum levels of T_3 , free

Fig. 1. Patterns of color flow Doppler sonography Four patterns are shown; pattern 0 (obtained from an AIT patient), Pattern I (obtained from a patient with mild Graves' disease), Pattern II (obtained from a patient with moderate Graves' disease) Pattern III (obtained from a patient with severe Graves' disease).

Table 1. Thyroid function of patients with AIT

Diagnosis	Age	Sex	Duration (months)	Dose (mg)	T3 (ng/dl)	fT3 (pg/ml)	T4 (μ g/dl)	fT4 (ng/dl)	TSH (μ U/ml)	TRAb (%)	Tg (ng/ml)	Anti-Tg	Anti-mc	Treatment
1 ARVD	37	M	38	150*	600	22	25.9	7.54	<0.1	14.1	2538	<100	<100	MMI
2 OMI	61	M	31	150*	710	27.7	22.6	10.1	<0.1	2.3	1660	<100	<100	MMI (Dis)
3 ARVD	43	M	24	150*	244	11.5	18.8	7.3	<0.1	0.5	169	<100	<100	MMI
4 DCM	27	M	24	150*	331	9.9	17.4	3.3	<0.1	1.4	440	<100	<100	(-)
5 OMI	68	F	37	100	193	5.7	14.6	2.95	<0.005	6.9	59			MMI
6 ARVD	69	M	48	200	170	6.9	14.3	3.2	<0.1	6.4	40			(-)
7 VT	61	M	37	150*	227	9.4	13.9	4.07	<0.1	8.1	71	<100	800	(-)
8 DCM	40	M	40	150*	200	5.7	13.1	2.98	<0.1	2	135	<100	<100	(-)
9 DCM	54	F	99	100	205		12.5		<0.005	3				PDN
10 OMI	70	M	10	150*	111	3.5	11.9	2.35	<0.1	0.3	5	<100	<100	(-)
11 DCM	51	M	37	200	140	4.8	11.4	2.63	<0.027	1	24	<100	<100	(-)
12 OMI	73	M	33	200	118	6	11.4	2.63		6.6	122			(-) (Dis)
13 OMI	70	M	52	100	135	5.6	10.5	2.86	<0.005	2.8	76.6	<100	<100	
Mean	55.7		39.2	150	260	9.9	15.3	4.3		4.3	445			
SD	15		20.9	35	186	7.4	4.7	2.5		4	803			

Dose and duration of amiodarone administration; 150 mg*: 100 and 200 mg on alternate days, TRAb: TSH receptor antibody, Tg: thyroglobulin, Anti-Tg: anti-thyroglobulin antibody titer, Anti-mc: anti-microsomal antibody titer, ARVD: arrhythmogenic right ventricular dysplasia, OMI: old myocardial infarction, DCM: dilated cardiomyopathy, VT: ventricular tachycardia, MMI: methimazole, PDN: prednisolone, Dis: amiodarone was discontinued

Table 2. Thyroid function of patients with AAH

Diagnosis	Age	Sex	Duration (months)	Dose (mg)	T ₃ (ng/dl)	fT ₃ (pg/ml)	T ₄ (μg/dl)	fT ₄ (ng/dl)	TSH (μU/ml)	TRAb (%)	Tg (ng/ml)	Anti-Tg	Anti-mc	Treatment
1 OMI	61	M	13	100	121	2.73	4.6	0.47	100.4		186			T4
2 ARVD	62	M	5	200		2.97		0.51	78	6.9	212			T4
3 DCM+CRF	53	M	1	100	115		6.7		22.2	5.2	186			T4
4 DCM	51	F	35	100	143	2.88	5.1	0.74	17.9	2.8	487	<100	<100	T4
5 ARVD	56	M	52	100	74		5.3		15.3	6.2	85	<100	<100	T4
6 HOCM	61	M	29	150*	74	2.37	3.8	0.74	14.2	13.6	54	<100	<100	T4
7 OMI	58	M	13	250		2.26		0.77	14			<100	<100	T4
8 OMI	65	M	31	100	142	3.3	7.3	0.9	13.5	0.1	225	<100	<100	T4
9 VT	28	M	9	100	106	2.5	6.2	1	13.2	5.4	190	<100	<100	T4
10 ARVD	29	M	27	100	97		7.2		11	3.9		<100	<100	T4
11 DCM	54	M	8	150*	114	2.9	5.3	0.7	10.4	6.3	235	<100	<100	T4
Mean	52.6		20.3	132	110	2.8	5.7	0.73	28.2	5.8	207			
SD	12.6		15.3	51	25	0.34	1.2	0.18	30.7	3.9	122			

The abbreviations are as indicated in Table 1. CRF: chronic renal failure, HOCM: hypertrophic obstructive cardiomyopathy

T₃, T₄, free T₄ and thyroglobulin had all increased to 260 ± 186 ng/dl, 9.9 ± 7.4 pg/ml, 15.3 ± 4.7 μg/dl, 4.3 ± 2.5 ng/dl, and 445 ± 803 ng/ml, respectively, in the AIT patients, accompanied by suppressed levels of TSH (<0.1 μU/ml). In the AAH patients, serum levels of total T₃ and T₄ were at the lower end of the normal range or slightly decreased, accompanied by increased serum levels of TSH (28.2 ± 30.7 μU/ml) and thyroglobulin (207 ± 122 ng/ml).

One of 13 patients with AIT was positive for TRAb. Furthermore, one of the 11 patients with AAH developed TRAb transiently. Anti-microsomal antibody was positive in one of 9 AIT patients, whereas anti-thyroglobulin antibody was negative in all AIT (n=9) and AAH (n=7) patients.

Consistent with a previous report [18], urinary excretion of iodide was also markedly increased in patients with AIT (6.5 ± 1.0 mg/gCr, mean $\pm$ SD, n=6) and AAH (7.0 ± 1.0 mg/g Cr, mean $\pm$ SD, n=4) than in normal subjects (0.31 ± 0.021 mg/g Cr), but there was no significant difference between levels in AIT and AAH patients ($P > 0.1$).

Ultrasound sonography and color flow Doppler sonography

The estimated thyroid volume was increased to 23.7 ± 5.6 ml in AIT (mean $\pm$ SD, n=10) and

21.2 ± 1.8 ml in AAH (mean $\pm$ SD, n=6), which was significantly smaller than in Graves' disease ($P < 0.05$). The internal texture of the thyroid in patients with AIT and AAH showed a decreased echogenicity with no nodular lesion. Consistent with a previous report [17], the pattern 0 was found in all patients with AIT (n=7). In patients with AAH, however, color flow varied from pattern 0 to II, depending on serum TSH levels. In contrast, patterns II and III were observed in patients with untreated Graves disease (n=10) (data not shown) [19].

Clinical course and treatment of AIH patients

The thyroid glands of AIT patients were almost all of the normal size or only slightly enlarged, except for case 1, in whom the thyroid gland was moderately enlarged. The thyroid gland was non-tender on palpation in all the AIT patients.

As shown in Table 1, four patients with marked thyrotoxicosis were treated with methimazole. Despite administration of this antithyroid drug, the increased serum levels of T₃ and T₄ persisted for a prolonged period. In one patient with arrhythmogenic right ventricular dysplasia (ARVD), who developed the severest AIT, accompanied by positive TRAb, serum levels of TSH were suppressed to less than <0.1 μU/ml for 9 months [13]. This TRAb

Fig. 2. Thyroid function of a patient with severe AIT, treated with methimazole. A 43-year-old-patient with arrhythmogenic right ventricular dysplasia (Table 1, case 3) developed moderate thyrotoxicosis 2 years after taking amiodarone. Methimazole (MMI) was prescribed, without discontinuing amiodarone. After three months, serum levels of T_3 and T_4 normalized, but serum level of TSH remained slightly elevated, even after one and a half years. Dotted areas indicate normal ranges of total T_4 (upper panel) and TSH (lower panel). Upper panel: $\blacktriangle$ — $\blacktriangle$; T_3 (ng/dl), $\blacksquare$ — $\blacksquare$; T_4 (μ g/dl), $\bullet$ — $\bullet$; Tg (ng/ml), Lower panel: $\bullet$ — $\bullet$; TSH (μ U/ml).

Fig. 3. Thyroid function of a patient with mild AIT, treated with prednisolone. A 54-year-old patient with dilated cardiomyopathy (Table 1, case 9) gradually became hypothyroid. L-thyroxine (T_4) was prescribed until October 1997, when mild AIT developed. Prednisolone was prescribed for two months, and the patient became euthyroid in a few months. The patient has been taking amiodarone continuously for the last 10 years. The dotted areas indicate normal ranges of total T_4 (upper panel), thyroglobulin (mid-panel), and TSH (lower panel). Upper panel: $\blacktriangle$ — $\blacktriangle$; T_3 (ng/dl), $\blacksquare$ — $\blacksquare$; T_4 (μ g/dl).

did not elicit any thyroid hormone-releasing activity, suggesting that the antibody developed after destructive thyroiditis [13]. Another 43-year-old patient

with ARVD was also treated with methimazole, without discontinuing amiodarone [20]. The thyrotoxicosis continued for more than 4 months,

Fig. 4. Thyroid function of a patient with mild AIT, which resolved spontaneously. A 69-year-old patient with arrhythmogenic right ventricular dysplasia (Table 1, case 6) developed mild AIT 4 years after starting amiodarone. The thyrotoxicosis resolved spontaneously without any treatment. The peak levels of total T_4 and fT_4 were $14.3 \mu\text{g/dl}$ and 6.9 pg/ml , respectively. The patient has been taking amiodarone continuously for the last 5 and half years. Dotted areas indicate normal ranges of free T_3 (upper panel), thyroglobulin (mid-panel) and TSH (lower panel). Upper panel: $\blacktriangle \cdots \blacktriangle$; fT_3 (ng/dl), $\blacksquare \cdots \blacksquare$; fT_4 (ng/dl).

Fig. 5. Thyroid function of a patient with asymptomatic AIT. A 70-year-old patient with old myocardial infarction (Table 1, case 10) was taking amiodarone for the last 3 years. Serum TSH decreased repeatedly to below $0.1 \mu\text{U/ml}$, but the patient is doing well, without any hyperthyroid symptoms. Dotted areas indicate normal ranges of total T_4 (upper panel), thyroglobulin (mid-panel), and TSH (lower panel). Upper panel: $\blacktriangle \cdots \blacktriangle$; T_3 (ng/dl), $\blacksquare \cdots \blacksquare$; T_4 ($\mu\text{g/dl}$).

accompanied with elevated serum levels of T_4 , T_3 , and Tg (Fig. 2). The serum level of TSH was suppressed to below $0.1 \mu\text{U/ml}$ for four months, and remained slightly high after 1 year, when all the medication was withdrawn. In the other two cases, the thyrotoxic period persisted for at least 3 months. After AIT completely resolved, serum level of TSH remained slightly high in three of four patients ($4\text{--}8 \mu\text{U/ml}$), suggesting that subclinical hypothyroidism persisted after a noticeable destructive process in the thyroid of these patients [21].

A female patient with sustained ventricular tachycardia due to dilated cardiomyopathy developed AAH after taking amiodarone for 4 years, and L-thyroxine was prescribed at a daily dose of $50\text{--}75 \mu\text{g}$ until April 1997, when mild AIT developed. Prednisolone was prescribed, without discontinuing the antiarrhythmic, and the thyrotoxicosis resolved in a few months (Fig. 3).

Eight patients developed mild (total T_4 ; $10\text{--}12 \mu\text{g/dl}$) to moderate thyrotoxicosis (total T_4 ; $12.5\text{--}17.4 \mu\text{g/dl}$), which subsided spontaneously in a few months without any treatment (Fig. 4). In the four mild AIT patients with asymptomatic thyrotoxicosis, serum levels of T_4 , fT_4 , T_3 , and fT_3 were in the upper normal range or slightly high, and the serum level of TSH was suppressed to below $0.1 \mu\text{U/ml}$, accompanied with increased thyroglobulin, suggesting a destructive type of thyrotoxicosis. In one patient, such a subclinical thyrotoxicosis had occurred twice in the last 4 years without any subjective symptoms (Fig. 5).

Eleven AIT patients continued amiodarone despite the drug-induced thyrotoxicosis without any additional adverse effects (Fig. 2–5), but two patients had to discontinue amiodarone, because of deterioration of pulmonary function ($n=1$) and multiple organ failure ($n=1$).

Clinical course and treatment of AAH patients

When AAH developed, the patients were simply supplemented with L-thyroxine. At a daily dose of $50\text{--}100 \mu\text{g}$ L-thyroxine, all of them remained euthyroid without discontinuing amiodarone.

Discussion

Although it is reported that AIT is less frequent in

areas where iodine intake is sufficient [11], we have observed 13 patients with AIT in the last 6 years. Recently it was postulated by Italian physicians that there are two types of AIT: namely, type I AIT, which develops in an abnormal thyroid gland with excessive synthesis of thyroid hormone, and is characterized by maintained or elevated ^{123}I uptake, ultrasound abnormalities (hypoechoic pattern and nodular lesions), and a normal to slightly high IL-6 level [22]. In contrast, type II AIT develops in an apparently normal thyroid, showing suppressed ^{123}I uptake, a normal ultrasound pattern, and a markedly increased IL-6 concentration, simulating destructive thyroiditis. There is as yet no general consensus on the treatment of AIT, but antithyroid agents are recommended for the treatment for type I, and glucocorticoids for type II AIT [1, 22]. From an endocrinological point of view, it is very important to quickly make a differential diagnosis of type I and type II AIT. Among several tests, ^{123}I uptake is the most reliable in making a differential diagnosis of types I and II [7], but it is not our practice to ask the patients to visit the hospital again only for differential diagnosis. Furthermore, serum levels of IL-6 may be overlapped in a few patients [18] and it takes a couple of weeks until the results arrive.

Increased serum levels of T_3 , T_4 and thyroglobulin, with suppressed serum levels of TSH, and negative thyroid hormone-releasing activity in the serum in the AIT patients [13] suggest that the thyrotoxicosis is not due to a stimulation-induced but due to a destruction-induced process. In an asymptomatic AIT patient, we observed that the serum level of TSH decreased to less than $0.1 \mu\text{U/ml}$ repeatedly in the last 4 years, suggesting that minimal destructive thyroiditis was exacerbated and subsided repeatedly. Very recently Pitsiavas *et al.* [23] demonstrated that amiodarone induces direct cytotoxic effects on rat thyrocytes *in vivo*, such as necrosis, apoptosis, marked lipofuscinogenesis and markedly dilated endoplasmic reticulum, reminiscent of endoplasmic reticulum storage disease. Presumably a clinically silent thyroiditis may lower the intrathyroidal amiodarone concentration, allowing the repair phase to proceed uninterrupted [24]. Whether such decreased serum levels of TSH or a suppressed response of TSH to TRH test [25] may predict the development of clinically overt AIT remains to be elucidated in a prospective study in a greater number of patients.

Very recently Bogazzi *et al.* [17] reported that differential diagnosis between type I and II AIT can be made rapidly by color flow Doppler sonography, by demonstration of hypervascularity in type I and absent or decreased vascularity in type II. In contrast to their observation that there were type I and type II AIT in 11 and 16 patients, respectively, we could not demonstrate any hypervascular lesion in our 13 AIT patients, suggesting that all the AIT patients we have seen so far had developed type II AIT. Such a greatly different incidence of AIT subtypes in Italy and Japan may be due to the different amount of iodine intake. If a patient has latent Graves disease in our country, he or she will easily manifest hyperthyroidism before any iodine-containing agent is prescribed. Furthermore, there are only a few patients with multinodular goiter which becomes autonomously thyrotoxic in our country [26]. In any event, iodine-induced hyperthyroidism is rarely seen in Japan [27, 28].

As expected, urinary excretion of iodide was greatly increased in both AIT and AAH patients. We could not demonstrate any significant difference between them. Nevertheless, if urinary iodide excretion is longitudinally measured in AIT patients, it may be increased in the thyrotoxic period, as demonstrated in the thyrotoxic phase of patients with painless thyroiditis [29].

As far as treatment for AIT is concerned, we have gained the impression that the antithyroid drug, methimazole, was not effective in ameliorating the thyrotoxicosis. In contrast, glucocorticoid seemed to rapidly ameliorate the thyrotoxicosis in one patient

with moderate AIT, but in 8 patients with mild to moderate AIT, the thyrotoxicosis spontaneously resolved in a few months without any treatment. We are of the same opinion as other clinicians concerning the administration of glucocorticoid to symptomatic AIT patients, if thyrotoxicosis is severe [1, 7, 22]. Whether other methods such as lithium and perchlorate are effective, remains to be evaluated in future studies [1, 7, 30].

In summary, since the introduction of amiodarone onto the market in 1992, AIT has been increasing in our country where iodine intake is still sufficient. When a patient taking amiodarone became thyrotoxic, ultrasonographic study and particularly color flow Doppler sonography is recommended for differential diagnosis of types I and II AIT. So far, all the AIT patients we have seen developed destruction-induced thyrotoxicosis (type II), which is unpredictable with an unexplained sudden onset. The rare incidence of type I AIT would be accounted for by a sufficient intake of iodine and a rare incidence of toxic multinodular goiter in our country. Amiodarone is not necessarily to be discontinued in patients with AIT as well as AAH, but the agent was discontinued in 2 of 23 patients in whom a severe extrathyroidal adverse reaction developed.

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