Thyroid Iodine Content Measured by X-Ray Fluorescence in Amiodarone-Induced Thyrotoxicosis: Concise Communication

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Iodine-induced thyrotoxicosis (IIT) is characterized by (a) a low radioiodine uptake, increased by exogenous TSH, and (b) a spontaneous evolution towards cure within a few months. An hypothetical pathogenesis of IIT is an initial inflation in the stores of thyroid hormones during iodine excess, followed by their sudden discharge into the circulation. Thyroid iodine content was measured by fluorescent scanning in 10 patients with amiodarone-induced thyrotoxicosis and in various control groups. Results were found to be high at the onset of the disease and to decrease during its course. The data agree with the hypothetical pathogenesis. Furthermore they may permit exclusion of a painless subacute thyroiditis, which is the main differential diagnosis of IIT.

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Iodine-induced thyrotoxicosis has been described both with apparently normal thyroid glands (*1*) and with previously abnormal thyroid glands (*2–4*). The sources of iodine excess are in most of the cases iodine-containing drugs. Amiodarone is an antiarrhythmic and antianginal drug that contains 38% (by weight) of iodine. It is responsible for most cases of iodine-induced thyrotoxicosis (*5–6*).

The mechanism of iodine-induced thyrotoxicosis is still unknown. It can be hypothesized that the physiopathological process consists in an initial inflation in the stocks of thyroid hormones, followed by their sudden discharge into the circulation. The aim of this paper is to report quantitative data on thyroid iodine contents as measured by x-ray fluorescence (*7–8*) in 16 amiodarone-treated patients. The results show that during treatment by amiodarone the thyroid iodine content of euthyroid patients was close to that of control values, whereas that of patients with thyrotoxicosis was significantly increased, suggesting an abnormality in the autoregulation of thyroid iodine content.

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MATERIAL

During a period of 1 yr we investigated the thyroid function of about 80 patients treated by amiodarone for cardiological problems, 30 of them with amiodarone-induced thyrotoxicosis (AiT). The thyroid function was evaluated either systematically or because of clinical evidence of hyperthyroidism. Fluorescent scanning of the thyroid could be performed in only 16 of these patients, who had been treated with amiodarone during 2 to 48 mo. Six of the 16 patients were euthyroid. Ten patients (9 males, 1 female) had AiT. In the latter group the thyroid iodine content was measured at the onset of the disease and was reassessed in seven cases during the course of the disease and/or after cure.

Fluorescent scanning was also performed in 12 patients with thyrotoxicosis induced by other sources of iodine excess: Benziodarone (3 cases), iodide (4 cases), lymphography (5 cases). In this group fluorescent scanning was performed only at the onset of disease.

Control groups were 18 euthyroid subjects and 28

patients with untreated Graves' disease, without iodine excess; these results have been published already (*9*).

METHODS

Diagnosis of thyrotoxicosis was based on elevated serum levels of T_3, T_4, RT_3-U and free thyroxine index (FTI), as assessed by the usual techniques. The biological criteria of thyrotoxicosis were stringent in AiT given that amiodarone decreases the peripheral conversion of T_4 to T_3 (*10*) and that FTI is usually high in euthyroid patients treated by amiodarone. Thus the diagnosis of thyrotoxicosis was based on a high level of T_3, and when necessary on the absence of elevation of serum TSH after i.v. injection of 400 μg TRH.

Iodine excess was measured by total serum iodine, according to a published method (*11*). Daily urinary iodine was measured by a modification of this method.

The responsibility of iodine excess in thyrotoxicosis was based on the following criteria (*1*): (a) onset of thyrotoxicosis during amiodarone therapy; (b) I-131 uptake lower than could be accounted for in a Graves' disease associated with amiodarone therapy; (c) I-131 uptake significantly increased by exogenous TSH; (d) absence of any thyroid pain, and no elevation of erythrocyte sedimentation rate; and (e) spontaneous evolution towards cure within a few weeks or months.

Antithyroglobuline and antimicrosomial antithyroid antibodies were looked for in every case.

Follow-up of patients. Amiodarone therapy was stopped as soon as the diagnosis was made. In six patients a spontaneous evolution was observed. Four patients were given medical therapy because of the severity of the thyrotoxicosis. Carbimazole seems to be useless (*1*). Therefore propylthiouracil was used for its known effect on peripheral deiodination of T_4 to T_3 (*12*). The criteria of thyroid recovery were: (a) biological euthyroidism, confirmed in six cases by a TRH test, and (b) normal I-131 uptake, given the possible persistence of iodine excess.

Fluorescent scanning was performed in all patients as soon as the diagnosis of AiT was made, and was repeated whenever possible during the course of the disease. Twenty-six measurements were made, with a procedure already described (*8*). The apparatus consists of an x-ray fluorescence unit (80-kV x-ray excitation beam plus Si (Li) semiconductor) mounted on the arm of a scanner. The detector axis is vertical and at 24° to the axis of the x-ray beam. Scintigraphic data are digitized on a data-processing unit. Determination of intrathyroid iodine was obtained from a calibration curve derived from tests on a thyroid phantom. As previously reported, with this system euthyroid patients averaged 15.6 ± 4.8 mg in the absence of goiter and 21.7 ± 11.0 in hyperthyroid patients without iodine excess (*9*).

RESULTS

Initial assessment of AiT. The ten patients with AiT were clinically thyrotoxic at first examination. No ophthalmopathy was observed. The thyroid gland was slightly larger and much harder than normal. Laboratory findings are given in Table 1. Hormone levels were high: FTI = 17.5 ± 7.5 (normal mean ± s.d. = 7.5 ± 1.5). T_3 = 421 ± 234 ng/dl (normal = 150 ± 15 ng/dl). Data concerning iodine excess were found to be: total serum iodine: 91.2 ± 55.2 μg/dl (normal = 5.0 ± 0.7 μg/dl); daily urinary iodine: 5.2 ± 3.6 mg/day (normal in France about 100 μg/day).

The mean I-131 24-hr uptake was 2.7 ± 1.4% (normal range 20–45%) and in seven cases was significantly reactivated by exogenous TSH up to 17.0 ± 8.1% ($p < 0.001$). Thyroid scintiscans after TSH showed a slightly hypertrophic gland.

No antithyroid antibodies were found present in any of the patients.

TABLE I. AMIODARONE-INDUCED THYROTOXICOSIS, INITIAL FINDINGS

Case no.	T_3 ng/dl	FTI	Total serum iodine g/dl	Urinary iodine mg/24 hr	I-131 thyroid uptake 24-hr % dose	
					basal	after TSH
1	858	18.3	115	7.1	1.0	9.0
2	—	20.0	—	6.0	3.0	—
3	222	13.1	34	0.5	2.4	27.7
4	—	34.0	—	6.0	2.5	18.0
5	598	13.6	105	—	3.8	9.0
6	174	10.4	171	12.0	4.3	21.0
7	575	22.6	100	4.0	2.1	—
8	310	22.0	—	—	1.0	—
9	343	9.5	22	1.1	5.4	25.2
10	284	11.5	—	5.0	1.8	9.0
Normal mean ± s.d.	150 ± 15	7.5 ± 1.5	5.0 ± 1.0	about 100 μg/d in France	2.7 ± 1.4	17.0 ± 8.1

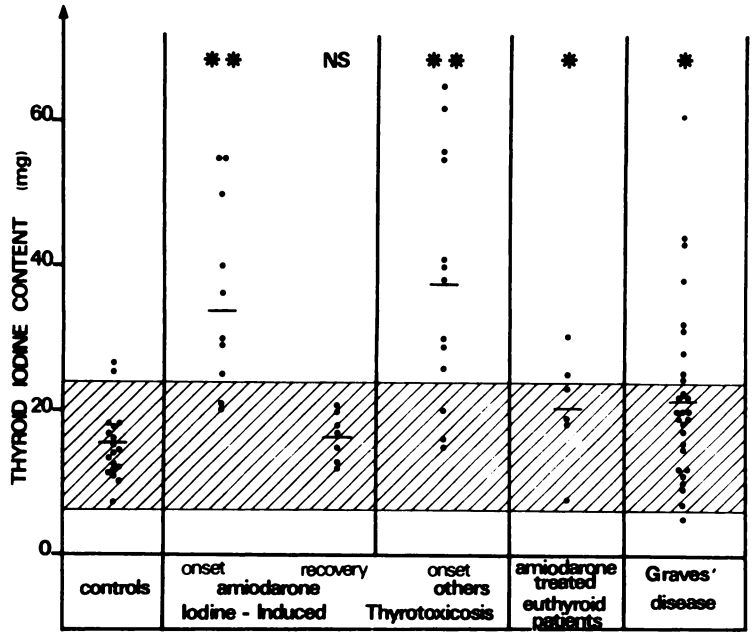

FIG. 1. Thyroid iodine content in amiodarone-induced thyrotoxicosis and in control groups. When compared with euthyroid patients without iodine excess, ** = $p < 0.001$; * = $p < 0.05$; NS = not significant.

Course of the disease in AiT. The untreated group was completely cured within 7.4 mo after diagnosis (limits 4–24 mo).

The medically treated group was cured within 7.8 mo (limits 5–12 mo). Propylthiouracil seemed to be effective in two cases, with a fall of serum T_3 within 4 to 5 days, and no apparent effect on serum T_4. In two cases propylthiouracil apparently had no effect.

Fluorescent scanning. Results are shown in Fig. 1. The initial thyroid content in AiT is high (mean ± s.d. = 34.1 ± 15.8 mg). This is not significantly different from the iodine content in patients with thyrotoxicosis induced by another source of iodine excess (35.7 ± 17.8 mg). Both values are significantly higher than in the group of euthyroid patients undergoing amiodarone therapy (20.7 ± 7.8 mg, $p < 0.05$); higher than in Graves' disease without iodine excess (21.7 ± 13.2 mg, $p < 0.05$); and higher than in euthyroid subjects without iodine excess (15.6 ± 4.8 mg, $p < 0.01$).

In seven cases of AiT the thyroid iodine content could be followed and was found to decrease. The mean interval between the first and the last fluorescent scanning was 3.5 mo (limits 5 wk–8 mo). The values obtained at the end of the disease (16.6 ± 3.4 mg) were found to be significantly lower than at the onset of the disease ($p < 0.01$ by paired t-test).

There was no evidence for any correlation between the following parameters: iodine content at the onset of the disease, rate of decrease of iodine content, severity of thyrotoxicosis, duration of the disease.

DISCUSSION

Under amiodarone treatment, most of the patients remain euthyroid and our results show that their thyroid iodine content is only slightly higher than those of euthyroid controls (*9*). This suggests that through the autoregulatory mechanism intrathyroid iodide concentration remains at a level that permits normal organic binding and hormonal synthesis (*13–14*).

When thyrotoxicosis occurs in amiodarone-treated patients, comparison of their thyroid iodine content with that of amiodarone-treated euthyroid patients suggests that thyrotoxicosis is the consequence of a failure of inhibition of iodine organification, leading to an excess of organified iodine. The thyrotoxicosis corresponds to the discharge of the hormonal stores into the circulation. The progressive decrease of total iodine content corresponds to the diminution of the stores of organified iodine.

Amiodarone is an organic iodinated compound. Its metabolism is as yet unknown. Whether it is hoarded by the thyroid—as in other tissues—and how and where it is deiodinated is not known. Thus our data in AiT as well as in other iodine-induced thyrotoxicoses suggest that the inflation of thyroid iodine content in AiT is due to the inflation of thyroid-organified iodine.

The incidence of AiT is poorly known. Given the widespread use of amiodarone, AiT seems to be rather rare. Whether AiT occurs in patients with an underlying thyroid abnormality is debatable. Although the thyroid function in our cases of AiT was not checked before thyrotoxicosis, no detectable abnormality was revealed after cure, including normal response of TSH to TRH. Thus it seems unlikely that autonomous thyroid tissue was present in our cases, as it has been suggested in other populations (*4*).

The diagnosis of Graves' disease occurring during amiodarone therapy was easily eliminated according to the following criteria (*1*): ophthalmopathy if present; higher I-131 uptake than in iodine-induced thyrotoxi-

cosis; no increase in the I-131 uptake by exogenous TSH; absence of spontaneous evolution towards cure within a few months. Furthermore, the total iodine content in most iodine-induced thyrotoxicoses is high, whereas most of patients with Graves' disease have a normal thyroid iodine content (*9,15*).

Iodine-induced thyrotoxicosis is easily distinguished from a subacute thyroiditis. In typical cases the clinical picture of subacute thyroiditis is different, with pain and high ESR. The thyroid iodine content is significantly lower than normal in subacute thyroiditis during the course of the disease, and thereafter it remains low for months, whereas it is higher than normal in iodine-induced thyrotoxicosis (*16*). Thus fluorescent scanning may be a useful differential tool for the diagnosis. It is much more difficult to distinguish AiT, and iodine-induced thyrotoxicosis in general, from painless transient thyroiditis. The overall picture is the same in both diseases, with thyrotoxicosis, absence of pain, normal or slightly high ESR and low I-131 uptake. The only difference, if any, is that iodine excess precedes iodine-induced thyrotoxicosis. The iodine content as measured by fluorescence x-rays during painless thyroiditis is not known. Thus it would be of considerable interest to investigate this point in order to distinguish—or to compare—painless thyroiditis and iodine-induced thyrotoxicosis.

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