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Acute Effects of Amiodarone Administration on Thyroid Function in Patients with Cardiac Arrhythmia

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ABSTRACT

Because little has been published on early effects of treatment with amiodarone on thyroid function, we studied serum total and free thyroid hormone, reverse T_3, and TSH levels in patients with cardiac arrhythmias during the first 10 days of treatment with a loading dose of amiodarone by iv infusion. Twenty-four patients were enrolled in the study. A standardized loading regimen for the iv infusion of amiodarone was used. The protocol provided the iv infusion of 20 mg/kg per day on day 1, the iv infusion of 10 mg/kg per day on day 2, then 600 mg/day *per os* for 7–10 days, and finally, in patients chronically treated with the drug, the dose was gradually reduced to 400–200 mg/day *per os*. Total and free concentrations of T_4 tended to progressively and significantly increase ($P < 0.0001$ repeated measures ANOVA) starting from the fourth day of therapy, whereas total T_3 decreased from the second day progressively ($P < 0.0001$) throughout the study; free T_3 did not significantly change. TSH levels early and significantly ($P < 0.001$, by ANOVA) increased throughout the study, starting from the first day of therapy and reaching at 10 days a value 2.7 times higher than the basal value. Reverse T_3 levels progressively and significantly (after 2 days of treatment) increased and paralleled the TSH values, reaching at the 10th day a value about 2 times higher than basal value. In conclusion, our data suggest that after iv treatment with amiodarone: 1) TSH is the first hormone to change significantly followed by reverse T_3, T_4, and T_3; 2) the progressive fall of T_3 levels reflects an inhibition of the peripheral conversion of T_4 to T_3; 3) the observed later increase of total and free T_4 levels may be explained by a contribution of direct thyroidal stimulation by TSH and/or by a reduction in T_4 clearance. (*J Clin Endocrinol Metab* **82:** 275–280, 1997)

AMIODARONE is a potent class III antiarrhythmic agent currently used for the treatment of supraventricular and ventricular arrhythmias unresponsive to conventional antiarrhythmic drugs (1–3). It contains 75 mg iodine/200 mg active substance with a long-term daily dose generally ranging from 600–200 mg. In view of its high iodine content, the drug was extensively studied for its possible influence on thyroid function (4–7). These studies demonstrated that amiodarone exerts important effects on peripheral metabolism of thyroid hormones and on thyroid function as well (1, 4). Amiodarone has been consistently shown to inhibit peripheral conversion of T_4 to T_3 *in vivo*, probably because of inhibition of 5′-deiodinase (type 1) activity (1, 3, 5–7). Using a double-tracer method, it has been shown (8, 9) that long-term therapy (lasting 6 months) with amiodarone, which is effective in suppressing arrhythmias, also reduces peripheral T_4-T_3 conversion. Although the previous data (6–9) clarified the effects of chronic therapy with amiodarone on thyroid hormone metabolism in patients, little information is available on the acute effects of this drug.

Earlier prospective studies on short-term effects of amiodarone have been limited to a small number of normal subjects rather than cardiac patients (10, 11), and/or did not include data on free hormone concentrations when performed in arrhythmic patients (12). Furthermore, most data (10–12) on TSH release were based on relatively a insensitive RIA method and/or TRH test, which was performed under basal condition and after 4 (10) or 24 (11) weeks of treatment, respectively. One prospective study examined patients with symptomatic ventricular tachyarrhythmias treated with oral doses of amiodarone and documented effects of the amiodarone at or after 7 days of treatment; this study did not evaluate free thyroid hormone levels (13).

Clinical interest in amiodarone has been increasing recently because of its effectiveness in a wide range of cardiac disturbances, including prophylaxis of life-threatening ventricular tachyarrhythmias in myocardial infarction survivors (sudden death cardiac prophylaxis), because it does not show the hemodynamic disadvantages of other antiarrhythmic drugs (14–16). More recent protocols of amiodarone treatment provide the use of an iv loading dose of the drug to rapidly reach an effective plasma concentration (14–17). However, to our knowledge, the mechanism of the acute interaction of the drug with the thyroid function is not well understood in amiodarone-treated arrhythmic patients.

We describe here a prospective study designed to gather information on acute changes in serum TSH and thyroid hormone levels after an iv loading dose of amiodarone in patients with cardiac arrhythmias; a group of well-matched

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patients, who were not treated with the drug, served as control group.

Methods

Hormone assay methods

Serum T_4 and T_3 concentrations were measured by the fully automated immunoenzymometric assay AIA 600 system (TOSOH Corp., Tokyo, Japan). Serum TSH was measured by a third-generation (sensitivity $\leq$ 0.005 μIU/mL immunoluminometric assay (ILMA) method BeriLux human TSH (Behringwerke AG, Marburg, Germany). Serum T_3 and T_4 free concentrations were measured using both the microparticle enzyme immunoassay by means of a fully automated IMx apparatus (Abbott Labs., Diagnostic Division, Abbott Park, IL) and the gel equilibration procedure (Liso Phase RIA system, Techno Genetics, Cassina de' Pecchi, Milano, Italy). Serum reverse T_3 (rT3) was measured by a RIA method (BIODATA Diagnostic, manufactured by Biodata S.p.A., Guidonia Montecelio, Roma, Italy). To minimize the assay error, each serum sample was assayed more than once in the same assay; consequently, the values used in the study are the mean result of all of these determinations. The sensitivity and between-assay precision of these methods were previously reported (8, 9).

In our laboratory the normal ranges for serum hormone concentrations are the following: total T_4: 58–154 nmol/L (4.5–12 μg/100 mL); total T_3: 1.2–3.0 nmol/L (80–200 ng/100 mL); free T_4: 9–24 pmol/L (7.0–18.5 pg/mL); free T_3: 3.9–8.3 pmol/L (2.6–5.4 pg/mL); TSH: 0.3–4.2 μIU/mL; rT_3: 0.14–0.55 nmol/L (9–35 ng/100 mL).

Amiodarone assay

Serum concentrations of amiodarone and its major metabolite *N*-desethyl-amiodarone were measured by a high performance liquid chromatography method, using as internal standard the trifluoperazine, as previously described in detail (17). Each unknown serum sample was triple assayed. The sensitivity of the assay is 0.15 μg/mL of amiodarone. We considered an acceptable therapeutical range to be when the serum amiodarone levels ranged from 0.5–2 μg/mL (2, 17).

Experimental subjects

Patients. Twenty-four patients who had been chosen for treatment with amiodarone because of their cardiac arrhythmia were sequentially enrolled in the study. The most important clinical data of these patients were reported in Table 1. Five patients showed overt cardiac failure (NYHA functional class $\geq$ III and/or left ventricular ejection fraction <20%, patients 1, 2, 6, 12, and 22 in Table 1); the other patients were in NYHA functional class < III or II with left ventricular ejection fraction $\geq$40%. Inclusion criteria were: 1) presence of cardiac arrhythmias evaluated by 48-h Holter monitoring; 2) documented inadequate efficiency of at least two different antiarrhythmic drugs; 3) absence of clinical, echographic, and laboratory evidence of thyroid diseases (including thyroid hormone concentrations and titers of antithyroid antibodies); and 4) no consumption of any other drug known to affect thyroid function. Myocardial contractility, dimensions, and function were assessed by two-dimensional echocardiography and radionuclide ventriculography. The weight of patients was monitored daily and did not significantly vary during the study.

Study protocol. Informed consent was obtained from all subjects, and the study protocol was approved by the local ethics commission (no one refused to participate to the study). The patients were hospitalized for the time necessary to perform the study. A standardized loading regimen for the iv infusion of amiodarone was used. The protocol provided for iv infusion of 20 mg/kg per day on day 1, iv infusion of 10 mg/kg per day on day 2, then 600 mg/day *per os* (200 mg at 0800 h, 1400 h, and 2000 h, respectively) for 7–10 days, and finally, in patients chronically treated with the drug, the dose was gradually reduced to 400–200 mg/day *per os*. When necessary, this therapeutical protocol was adjusted

TABLE 1. Main clinical parameters of studied patients

Treated patients	Gender	Age (yr)	UCD	Arrhythmia	NYHA class	Total T_4 (μg/100 mL)	Total T_3 (ng/100 mL)	Free T_4 (pg/mL)	Free T_3 (pg/mL)	TSH (μUI/mL)
1	M	76	CAD	AF	III–IV	5.3	67	7.9	2.3	4.1
2	M	63	CAD	AF + CVA	III	5.3	100	5.7	3.8	3.8
3	F	64	CAD	AFL	I	5.3	103	7.3	3.3	2.3
4	M	54	CAD	AF	I	8.3	82	10.7	2.8	1.1
5	F	62	CAD	AF + CVA	I	7.8	98	9.2	3.7	2.4
6	M	74	VDCM	AF	III	7.8	66	8.2	2.7	4.0
7	F	83	CAD	AF	I	10.7	116	8.8	3.7	3.0
8	M	65	CAD	CVA	II	9.4	97	15.3	4.2	0.7
9	M	44	CAD	CVA	I	8.2	119	14.0	4.5	1.3
10	F	81	CAD	AF	I–II	9.9	105	15.2	4.9	2.1
11	M	70	CAD	AF	I	6.1	99	10.4	2.8	2.2
12	M	53	VDCM	CVA	III	6.6	76	10.8	3.5	0.6
13	F	76	CAD	AF	II	8.8	122	15.3	4.5	1.0
14	M	66	CAD	CVA	II	6.0	87	8.7	2.7	1.7
15	M	73	CAD	CVA	I	8.0	124	10.0	4.8	1.8
16	M	72	CAD	CVA	II–III	9.9	120	14.9	3.7	1.0
17	F	70	CAD	CVA	I	10.0	140	16.3	4.5	0.6
18	M	68	SSS	CVA	I	8.7	147	9.4	2.9	4.1
19	F	68	CAD	AF	I–II	8.8	106	14.1	2.7	2.7
20	M	73	CAD	CVA	II–III	8.3	83	12.7	3.0	2.7
21	M	72	CAD	CVA	II	9.1	94	12.5	1.9	0.8
22	M	50	VDCM	CVA	III	4.0	89	6.3	5.0	1.3
23	F	64	IDCM	CVA	II	7.9	128	10.6	4.7	1.9
24	F	66	CAD	AFL	II	7.6	84	12.7	2.4	4.1
Mean		67.0				7.83	102.2	11.13	3.54	2.14
SD		9.5				1.75	21.5	3.11	0.93	1.20
Controls	14 M + 6 F									
Mean		66.6				7.95	96.9	10.71	2.90	1.61
SD		9.8				1.60	17.7	2.77	0.80	0.88

UCD, Underlying cardiac disease; CAD, coronary artery disease; AF, atrial fibrillation; AFL, atrial flutter; CVA, complex ventricular arrhythmias; VDCM, valvulopatic dilated cardiomyopathy; IDCM, idiopatic dilated cardiomyopathy; SSS, sick sinus syndrome. Hormone concentrations are mean of two different samples collected before start of amiodarone treatment.

in each patient, following the results of amiodarone assay, to reach a relative plateau of serum amiodarone within the therapeutical range without increasing drug values above the limit toxic level (*i.e.* 2.5 μg/mL).

In all 24 patients studied, two serum samples for amiodarone and hormonal assays were collected before the start of therapy (basal sample), and then other serum samples were collected at least every 12 h in the first 2 days after amiodarone administration and at least once a day in the following days. In 16 patients who had been hospitalized for a long time because of their cardiac disease, serum samples were also collected at 0800 h of the 10th day. Finally, in 16 patients who had been chronically treated with amiodarone, at least one other serum sample was collected 3 months after the start of therapy.

Control group. Twenty arrhythmic patients (14 men and 6 women), matched for age (66.6 ± 9.8 yr; range 46–81 yr) and gender, as well as for underlying heart disease, were enrolled in the study as the patients' control group. These patients were hospitalized in the same clinical ward and for the same period of the study as the amiodarone-treated patients; these patients, even if they suffered from cardiac arrhythmias, were not given for treatment with amiodarone and did not take any medications that may have affected thyroid function.

Serum samples for hormone assays were collected throughout 5 consecutive days in the clinical ward.

Statistical analysis

The statistical analysis was carried out by a Macintosh IIsi personal computer using the Stat-View 4.0 and SuperANOVA programs (Abacus Concepts, Berkeley, CA). Data were analyzed by ANOVA for paired data (repeated measures), and the significant differences between the pairs of means were tested by the Bonferroni/Dunn test for paired data. The results were expressed as the mean ± SD in the text and as the mean ± SEM in the figures.

Results

Control patients

There was no significant variation in serum concentrations of TSH and of thyroid hormones (total and free concentration) throughout the 5 days of the study in the arrhythmic patients not treated with amiodarone (data not shown). Moreover, the mean hormone levels of these patients were not significantly different from basal hormone values found in patients treated with amiodarone (Table 1).

Amiodarone-treated patients

Baseline hormone values. On average, basal levels of total and free thyroid hormones and TSH were found to be in the normal range (Table 1). However, as expected (18, 19), the analysis of individual values indicates that several patients (with NYHA functional class ≥ III) showed evidence of euthyroid sick syndrome, as demonstrated by low levels of both total and/or free T_3 and/or T_4 concentrations (patients 1, 2, 6, 12, and 22 in Table 1).

Serum drug levels. The mean (± SEM) time course of serum amiodarone and of its main metabolite *N*-desethyl-amiodarone throughout the first 10 days of therapy in patients treated with amiodarone is shown in Fig. 1. The peak of amiodarone concentration observed in the first 12–36 h was caused by the loading iv dose of the drug. It is important to note that a detectable concentration of the main and pharmacologically active metabolite was on average found within 24 h after the start of amiodarone administration. By using the therapeutical protocol described in this study, the plateau

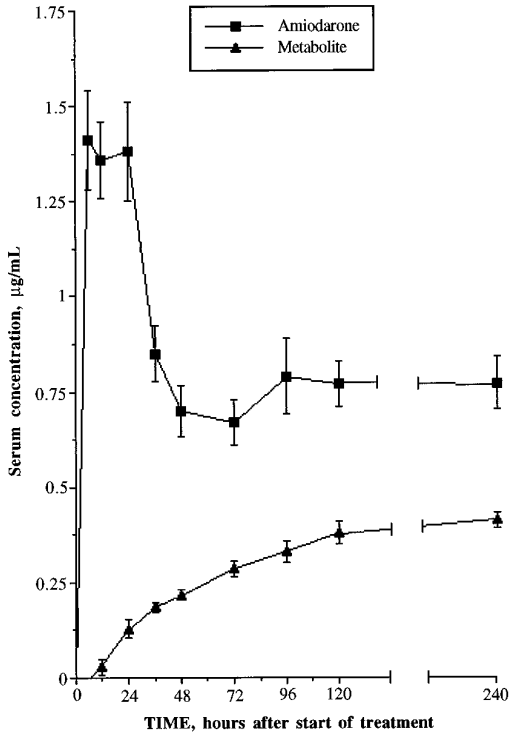

FIG. 1. Mean (±SEM) time courses of serum amiodarone and its main metabolite *N*-desethyl-amiodarone observed in treated patients throughout the study.

of the circulating levels of amiodarone was generally reached in 5–12 days (on average in 9 days) (Fig. 1). The mean concentration of amiodarone after 3 months of therapy was 0.73 ± 0.25 μg/mL, and that of its metabolite was 0.63 ± 0.11 μg/mL; the mean ratio, found in chronically treated patients (for at least 3 months) between *N*-desethyl-amiodarone and amiodarone concentrations was 0.84 ± 0.34. All of these findings are consistent with previously described data (17).

Serum hormone levels after amiodarone therapy

Acute effects of amiodarone administration. The time courses of the daily mean values of serum total and free T_3 and T_4 concentrations, observed in the first 10 days of therapy with amiodarone, are shown in Figs. 2 and 3, respectively. Total and free concentrations of T_4 tended to significantly ($P < 0.0001$, by ANOVA) increase in the first 5 days of therapy, reaching a maximum at the fifth day after the start of therapy (free T_4 = +15.3% and total T_4 = +11.5%, on average, compared with basal values). On the contrary, total T_3 levels progressively and significantly fell throughout the study ($P < 0.0001$, by ANOVA), whereas free T_3 did not significantly change. However, after 10 days of therapy, the free T_3 levels were, on average, 88.4%, and the total T_3 were 81.3% compared with basal values.

The time courses of daily mean values of serum TSH and rT_3 concentrations, observed in the first 10 days of therapy with amiodarone, are shown in Fig. 4. TSH levels early and significantly ($P < 0.001$, by ANOVA) increased throughout the study, starting from the first day of therapy and at 10 days reaching a value that was on average 2.7 times higher than

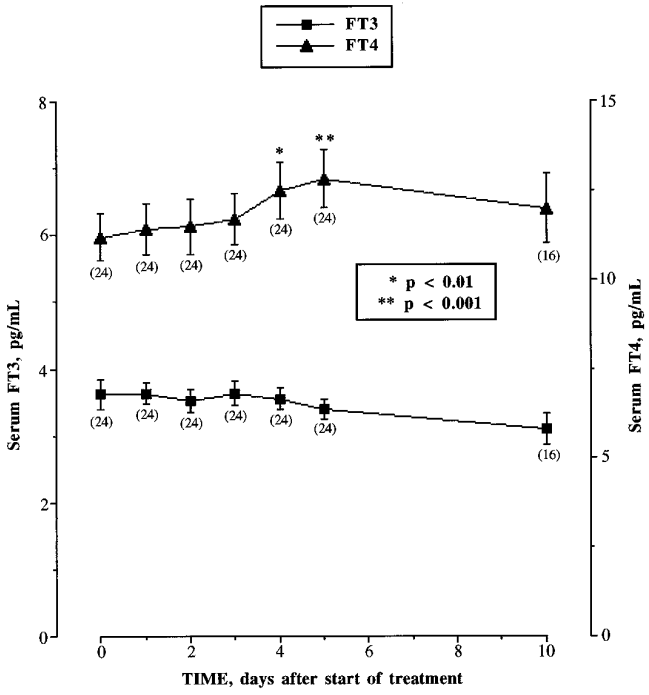

FIG. 2. Time courses of mean (±SEM) daily values of serum free T_3 and T_4 concentrations observed in first 10 days of therapy with amiodarone in patients with cardiac arrhythmia. Number of patients studied on each day is shown in parentheses. Statistical significance (by Bonferroni/Dunn test after ANOVA, repeated measures) compared with basal values is also noted.

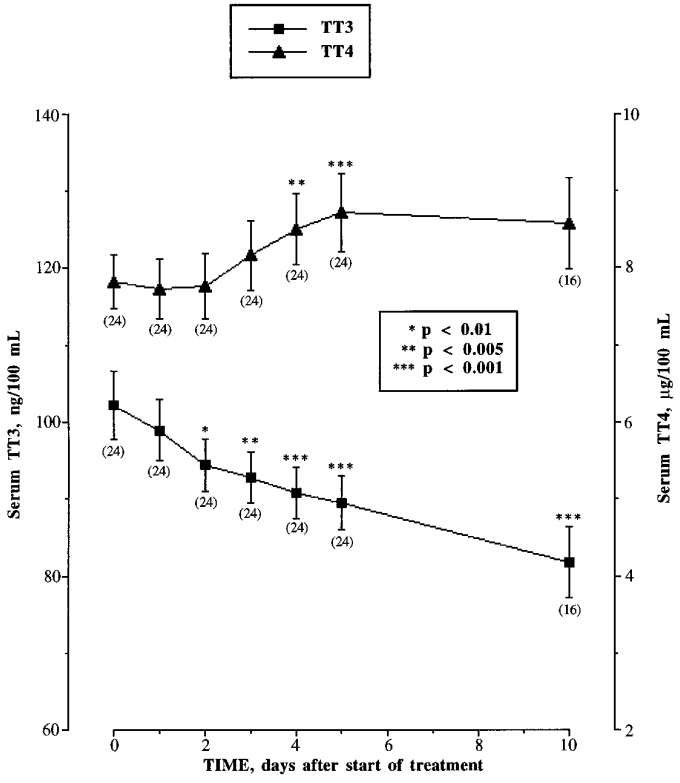

FIG. 3. Time courses of mean (±SEM) daily values of serum total T_3 and T_4 concentrations observed in first 10 days of therapy with amiodarone in patients with cardiac arrhythmia. Number of patients studied in each day is shown in parentheses. Statistical significance (by Bonferroni/Dunn test after ANOVA, repeated measures) compared with basal values is also noted.

the basal value (Fig. 4). rT_3 levels progressively and significantly (after 2 days of treatment) increased and paralleled the TSH values, at the 10th day reaching a value that was about two times higher than basal value (Fig. 4).

Chronic effects of amiodarone therapy. In the 16 patients who were able to continue the amiodarone treatment for more than 3 months, mean serum TSH (5.8 ± 7.9 μIU/mL *vs.* 2.6 ± 2.2 μIU/mL, $P < 0.001$) and rT_3 (67.5 ± 23.0 ng/100 mL *vs.* 30.8 ± 11.0 ng/100 mL, $P < 0.0001$) were higher than basal value, whereas total T_3 remained significantly lower than basal value (88.9 ± 21.4 ng/100 mL *vs.* 102.2 ± 21.5 ng/100 mL, $P < 0.001$). Moreover, mean serum free T_3 tended to come back to basal value (3.8 ± 1.0 pg/mL *vs.* 3.5 ± 0.9 pg/mL), whereas T_4 values were found to be slightly higher than basal value (total T_4: 8.8 ± 2.1 μg/100 mL *vs.* 7.8 ± 1.8 μg/100 mL, and free T_4: 12.1 ± 3.2 pg/mL *vs.* 11.1 ± 3.1 pg/mL, respectively).

Discussion

Only a few studies (10, 11) have investigated the early effects of amiodarone on thyroid function. One study was performed in nine healthy young adult subjects (all men, aged 25–40 yr), who received 400 mg *per os* for 28 days (10). This protocol did not provide the time courses of free concentrations of thyroid hormones (only serum free T_3 was measured 11 days before and at 2 and 28 days after commencement of treatment) and amiodarone or its main metabolite during the early days of treatment with the drug. Furthermore, the protocol of amiodarone administration differs markedly from that currently employed in the treatment of patients with cardiac arrhythmias (2, 14–16). In fact, because of the long biological half-life of amiodarone, a loading dose of drug is currently recommended to rapidly reach therapeutic circulating levels of the drug (2, 14–17). Moreover, although there is a linear relationship between oral doses of amiodarone and drug concentrations in plasma and myocardial tissue, the concentrations in patients taking the same dose vary markedly, and therefore monitoring drug concentration is considered important to achieve maximal therapeutic effects and to minimize possible side effects (14–17). For these reasons, the results found in the previous study (10) in normal subjects may be not directly extrapolated to arrhythmic patients treated with modern-day regimens of amiodarone.

Our studies describe the early effects of amiodarone treatment in arrhythmic patients. Our findings indicate that in arrhythmic patients short-term amiodarone treatment induced a significant decrease in serum total T_3. Interestingly, in our patients free T_3 showed a pattern not parallel to that of total T_3, mainly in the first 4 days of treatment (Fig. 2). The basis for this observation is not known. This finding may reflect the displacement by amiodarone of T_3 bound to serum proteins (15).

It is noteworthy that, unlike previous data in normal sub-

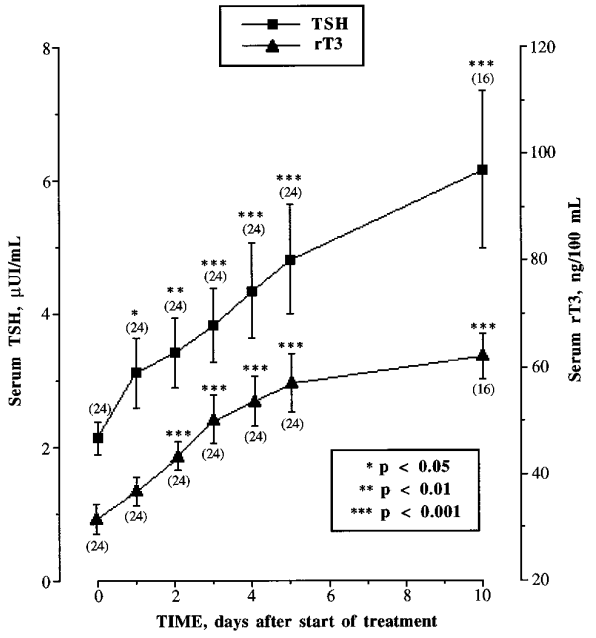

FIG. 4. Time courses of mean (±SEM) daily values of serum rT_3 and TSH concentrations observed in first 10 days of therapy with amiodarone in patients cardiac arrhythmia. Number of patients studied in each day is reported in parentheses. Statistical significance (by Bonferroni/Dunn test after ANOVA, repeated measures) compared with basal values is also noted.

jects (10), which showed an early decline in T_4 concentrations, our data showed a significant increase in plasma T_4 (both total and free) with the drug; a similar tendency for total T_4 increase was also previously observed in arrhythmic patients after 7 days of treatment with an oral dose of amiodarone by other authors (13). The early decline of T_4 concentrations in normal subjects given amiodarone has been suggested to be responsible for the subsequent increase in TSH (20). However, our data do not support this possibility.

We have documented a rise in serum TSH concentration in our patients earlier (first day) than previously reported in normal subjects (second day) (10) or arrhythmic patients (eighth day) (12). It is not clear whether this discrepancy can be related to the different modality (oral *vs.* iv) and/or amount of drug administration, improved TSH techniques, the difference in the study population, and/or a more frequent collection of blood samples in the first days of the study. Indeed, by frequent sampling, we were able to clearly show that TSH is the first hormonal parameter to be affected by amiodarone administration. The use of a third-generation assay for TSH measurement provided a suitable sensitivity to determine the minimal hormonal changes observed after amiodarone treatment. An increment of 39%, on average, was found in serum TSH at 24 h of treatment, and a significant increment (65%) of TSH levels was clearly demonstrated on the second day of amiodarone administration (Fig. 4). The basis for the measured TSH increase after amiodarone is not known. It may be caused by an early inhibition of type II 5′-deiodinase in the pituitary cells; other possible effects may include a direct TSH secretory effect of the drug and a competition between amiodarone, its metabolite, and specific nuclear receptors for T_3 (3). In this respect, there are indications that desethylamiodarone (and not amiodarone) competes with T_3 for receptors in most tissues (21). Our data showing a rapid appearance of desethylamiodarone in plasma within 24 h after iv amiodarone, and the parallel rise with the rise of TSH levels lend further support to this possibility.

The later increase in the serum total T_4 and free T_4 levels (which reach statistical significance at 4 days) may be explained by a direct stimulation of T_4 secretion by increased TSH. However, in the absence of kinetic studies, it is not possible to exclude an important role of an alteration in T_4 to T_3 metabolism (5).

The progressive significant increase in rT_3, as well as the concomitant and parallel fall in serum total T_3 levels, which reach a statistical significance after 48 h of treatment, suggest an inhibition by amiodarone or its metabolite of type I 5′ deiodinase resulting in a decrease in peripheral conversion of T_4 to T_3 and metabolic clearance of rT_3.

The inhibitory action of amiodarone on iodothyronine deiodinase activity seems to persist during chronic treatment with the drug, as demonstrated by a persistent increase of TSH and rT_3 associated with some decrease in total T_3 concentrations. This is in accordance with our previous double-tracer kinetic study in which a direct measurement of T_4 to T_3 conversion was performed before and during chronic amiodarone treatment, and an inhibition of T_4 to T_3 peripheral conversion was demonstrated (9). These alterations in thyroid hormone metabolism may contribute to changes observed during the first 24–120 h after amiodarone iv loading dose in this study.

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NIH CONSENSUS DEVELOPMENT CONFERENCE: MANAGEMENT OF HEPATITIS C March 24–26, 1997

Natcher Conference Center The William H. Natcher Building National Institutes of Health Bethesda, Maryland

Sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases, National Heart, Lung, and Blood Institute, National Institute on Drug Abuse, Centers for Disease Control and Prevention, and the NIH Office of Medical Applications of Research

Management of Hepatitis C is the subject of an upcoming consensus development conference sponsored by the National Institutes of Health (NIH). The conference is scheduled for March 24–26, 1997, in the Natcher Conference Center and is open to the public.

The purpose of the conference is to reach agreement on Management of Hepatitis C. Key questions to be addressed are:

- What is the natural history of hepatitis C?
- What is the most appropriate approach to diagnose and monitor patients?
- What recommendations can be made to patients to prevent transmission?
- Which patients should be treated?
- What is the most effective approach to therapy?
- What are the most important areas for future research?

The conference will bring together specialists in virology; epidemiology; and natural history, prevention, and therapy of hepatitis C; as well as members of the public, and other relevant fields. On the first 2 days, experts will present current scientific thinking about the diagnosis, management, and prevention of hepatitis C, and concerned voluntary organizations will be invited to make statements. On the third day, after considering the scientific evidence, the consensus panel will present its draft report and invite comments from the audience. Donald W. Powell, M.D., Professor and Chairman, Department of Internal Medical, University of Texas Medical Branch at Galveston, will chair the panel.

To register for the Consensus Development Conference on Management of Hepatitis C or to obtain further details, contact: Conference Registrar, Technical Resources International, Inc., 3202 Tower Oaks Boulevard, Rockville, Maryland 20852. Phone: 301-770-0610; Fax: 301-468-2245; E-mail: confdept@tech-res.com.