

Effect of Amiodarone on Serum Triiodothyronine, Reverse Triiodothyronine, Thyroxin, and Thyrotropin

A DRUG INFLUENCING PERIPHERAL METABOLISM OF THYROID HORMONES

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ABSTRACT 2-*n*-Butyl-3-(4'-diethylaminoethoxy-3',5'-diiodobenzoyl)-benzofurane (amiodarone), a drug used in arrhythmias and angina pectoris, contains 75 mg of organic iodine/200 mg active substance. Four studies were performed to test its effect on thyroid hormone metabolism: (a) nine male subjects were treated with 400 mg of amiodarone for 28 days; (b) five male subjects received, for the same period of time, 150 mg of iodine in the form of Lugol's solution; (c) five subjects received 300 μ g L-thyroxine (T_4) for 16 days; from the 10th to the 16th day, 400 mg of amiodarone was added; and (d) five euthyroid subjects received 300 μ g L- T_4 for 16 days. The changes in serum thyroid-stimulating hormone (TSH), serum total T_4 , 3,5,3'-triiodothyronine (T_3), free T_3 , and 3,5,3'-triiodothyronine (reverse T_3 , rT_3) were measured, and the pituitary reserve in TSH was evaluated by a thyrotropin-releasing hormone (TRH) test.

The results show that amiodarone induced a decrease in serum T_3 (28 ± 5.1 ng/100 ml, mean \pm SEM, $P < 0.05$), whereas serum T_4 and rT_3 increased (1.4 ± 0.4 μ g T_4 /100 ml, NS and 82.7 ± 9.3 ng rT_3 /100 ml, $P < 0.01$). The control study with an equal amount of inorganic iodine did not induce these opposite changes but slightly lowered serum rT_3 , T_3 , and T_4 . In the third study, serum rT_3 increased as under amiodarone treatment, thereby proving that these changes were peripheral. It is suggested that amiodarone changes thyroid hormone metabolism, possibly by reducing deiodination of T_4 to T_3 and inducing a preferential production of rT_3 .

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Amiodarone also increased the response of TSH to TRH. The maximal increment of serum TSH above base line was 32 ± 4.5 μ U/ml under treatment and 20 ± 3 μ U/ml before treatment ($P < 0.01$). During this test, the serum T_3 increase was more pronounced than during the control period (83 ± 13 and 47 ± 7.4 ng/100 ml, $P < 0.05$).

INTRODUCTION

2-*n*-Butyl-3-(4'-diethylaminoethoxy-3',5'-diiodobenzoyl)-benzofurane (amiodarone)¹ is an antiarrhythmic and antianginal drug used widely on the European continent (1). It contains 75 mg iodine/200 mg active substance, the average daily dose being 400–600 mg.

In view of its high iodine content, the drug was selected to study its influence on thyroid function. In particular, its effect on the metabolism of thyroxine (T_4)² was studied, with serum 3,5,3' triiodothyronine (T_3) and 3,3',5' triiodothyronine (reverse T_3 ; rT_3) as the peripheral products of T_4 metabolism. It was found that this drug reduced serum T_3 and increased serum rT_3 and T_4 . To prove that its effect was peripheral, the study was repeated in T_4 -treated subjects.

METHODS

Clinical studies. All subjects, aged 25–40 yr, were male and gave informed consent to the study. Family history for

¹ Cordarone, Labaz Inc., Brussels, Belgium.

² *Abbreviations used in this paper:* rT_3 , reverse T_3 (3,5,3'-triiodothyronine); T_3 , 3,5,3'-triiodothyronine; T_4 , thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

thyroid disease was negative. The thyroid glands were inspected by palpation, and in the amiodarone study thyroid scans with ^{99}Tc were performed. Amiodarone can induce corneal deposits, unnoticed by the subject but detectable by slit lamp examination (2). All subjects received an ophthalmologic examination before and after treatment. Pulse rate and the morning rectal temperature were measured in the subjects receiving T_4 and amiodarone.

Study with amiodarone alone. Nine subjects received 400 mg amiodarone for 28 days. Blood samples were obtained on the 11th and the day before the start of treatment and then 2, 4, 6, 14, and 28 days thereafter. The intravenous thyrotropin-releasing hormone (TRH) test with 0.2 mg TRH (Hoffmann-La Roche, Basel, Switzerland) was performed 11 days before and on the 28th day of treatment. For this test the subjects were recumbent, and blood was sampled at -15, 0, 20, 30, 60, and 120 min.

Study with Lugol's solution. Five subjects received 13 drops of a freshly prepared 5% Lugol's solution twice a day. The daily iodine supplement amounted to 150 mg. The experimental protocol was identical to the one with amiodarone alone, but all blood samples were obtained with the subject recumbent.

Study with thyroxine and amiodarone. Five subjects were studied. 300 μg L- T_4 (Eltroxine, Glaxo Laboratories, Ltd., Greenford, England) alone was given for 10 days and then supplemented with 400 mg amiodarone. Blood was obtained from a recumbent subject the day before (day 9), at the beginning of amiodarone (day 10) and 2, 4, and 6 days after starting the combined treatment (days 12, 14, and 16). On the 6th day of amiodarone treatment, a TRH test was performed.

Study with thyroxine. Six euthyroid subjects were given 300 μg L- T_4 daily for 16 days. Blood was obtained at the same moments as in the study with thyroxine and amiodarone.

Laboratory procedures. The radioimmunoassays of serum T_4 and T_3 were performed according to Mitsuma et al. (3) in a slightly modified form (4, 5). rT_3 was measured in 0.1 ml serum with a specific radioimmunoassay (6). The least detectable concentration, resulting in a response 2 SD away from the zero dose response, was 10 ng/100 ml. The

within and interassay variability was 6 and 8%, respectively. TSH was also determined by radioimmunoassay (7). The thyroxine-binding globulin capacity for T_4 was measured according to Roberts and Nicolai (8). The normal values (mean \pm 2 SD) for serum T_4 were 8.2 ± 3.9 $\mu\text{g}/100$ ml, for T_3 165 ± 46 ng/100 ml, and for rT_3 45 ± 20 ng/100 ml. The fraction of serum free T_3 was determined by equilibrium dialysis, the normal value being $0.169 \pm 0.11\%$ (9). The normal range for serum TSH was from < 0.5 to 6 $\mu\text{U}/\text{ml}$.

Statistical analysis. The results were expressed as the mean \pm SEM. Significance was calculated by the paired Student's *t* test and one-way analysis of variance (10).

RESULTS

In vivo and in vitro, amiodarone did not alter the results of the T_3 , rT_3 , and T_4 radioimmunoassays. In vitro, up to 50 $\mu\text{g}/100$ ml amiodarone was without any effect on the three assays. To test its influence in vivo, a hypothyroid subject, treated by a single morning dose of 100 μg T_3 (Cytomel Smith Kline & French Laboratories, Philadelphia), received 400 mg amiodarone per day for 6 days. The fasting serum T_3 concentration varied slightly (220 before and 195 ng $\text{T}_3/100$ ml after 6 days of treatment), and the serum rT_3 remained unmeasurable. The thyroxine-binding globulin capacity was measured in the sera of the subjects receiving 300 μg L- T_4 and 400 mg amiodarone. It remained unchanged (18 ± 0.8 before and 17.1 ± 1 μg $\text{T}_4/100$ ml on the 6th day of treatment). Hence methodological artifacts due to the drug were excluded.

The subjects did not report side effects, and clinical examination did not reveal any modification in thyroid size. Pulse rate and rectal temperature did not change in the group receiving L- T_4 and amiodarone. A slight corneal deposit developed in one subject. The lesion had disappeared 3 mo after stopping the drug.

5 mo after ending the treatment, one 26-yr-old subject developed marked hyperthyroidism of 2-3 mo duration. The disease disappeared without treatment.^a

Study with amiodarone alone. These studies are shown in Fig. 1. The mean serum T_3 concentration increased slightly but significantly during the control period (day -11, 166 ± 6 ; day -1; 184 ± 8 ng/100 ml; $P < 0.05$). The first blood samples were obtained from recumbent subjects; all others while the subjects were sitting; this possibly explains the difference. In all subsequent studies blood was obtained recumbent. To reduce the statistical effect of the high serum T_3 at day -1, all samples before and during treatment were compared by analysis of variance. They were found to be significantly different ($P < 0.05$). On the 28th day of treatment, the serum T_3 levels were 28 ± 5.1 ng/100 ml, lower than the serum T_3 level 11 days before treatment ($P < 0.05$). These changes were still within the normal range of the serum T_3 concentration. The free serum T_3 fractions

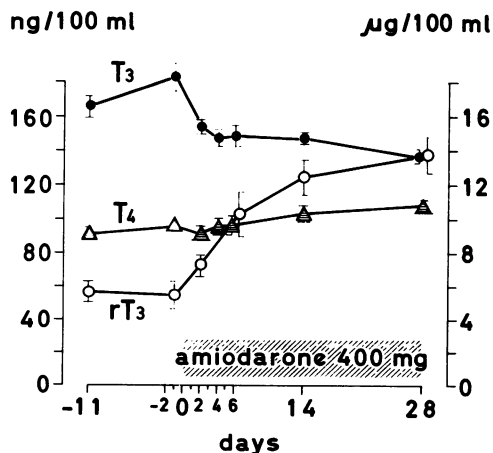


FIGURE 1 Effect of 400 mg amiodarone daily on thyroid hormone serum concentration: Δ , T_4 in micrograms per 100 ml; \bullet , T_3 in nanograms per 100 ml; and \circ , rT_3 in nanograms per 100 ml.

^a To be published.

TABLE I
Basal Serum TSH during Amiodarone Treatment

	Before treatment	Day of treatment				
		2	4	6	14	28
				$\mu U/ml$		
Mean	4.4	5.6	8.7*	11.0*	8.9*	5.6
SEM	0.5	0.6	1.6	1.1	1.7	1.1

* Values significantly elevated ($P < 0.05$).

were measured 11 days before and 2 and 28 days after commencement of treatment. They were $0.138 \pm 0.06\%$, $0.136 \pm 0.1\%$, and $0.136 \pm 0.07\%$, respectively (NS). The converse changes were seen with serum rT_3 . Its serum concentration increased immediately with amiodarone treatment. 28 days later, the serum rT_3 had increased by 82.7 ± 9.3 ng/100 ml ($P < 0.01$). The concentration was 2.2 times higher than before treatment and well above the normal range.

The serum T_4 concentration dropped during the first days of treatment and increased slightly thereafter. By the 28th day the increase was 1.4 ± 0.4 $\mu g/100$ ml. Serum TSH increased in the first 6 days of treatment and then returned to initial serum concentrations (Table I). A marked and significant increment in the TSH response to TRH was seen under amiodarone treatment

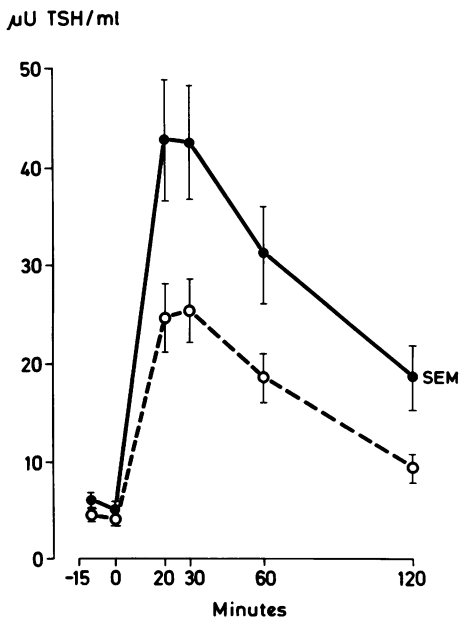


FIGURE 2 Serum TSH concentrations after 0.2 mg TRH i.v. before (interrupted line) and after 28 days of amiodarone treatment (solid line). With the exception of the basal serum TSH concentration, all serum TSH concentrations were significantly higher ($P = 0.05-0.001$) under amiodarone treatment.

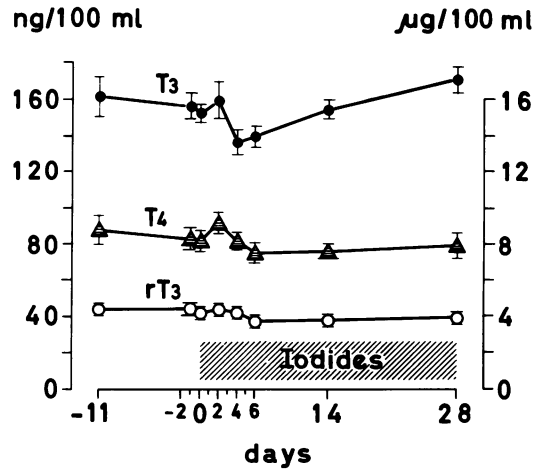


FIGURE 3 Effect of 13 drops of Lugol's solution twice a day (150 mg iodine) on thyroid hormone serum concentrations. For the symbols, see Fig. 1.

(Fig. 2). The difference between the mean basal and the highest TSH concentration (Δ max TSH) was 32 ± 4.5 $\mu U/ml$, compared to 20 ± 3 $\mu U/ml$ during the control phase. The increased TSH secretion resulted also in a greater rise of serum T_3 . The mean absolute increase in T_3 (Δ max T_3) was 47 ± 7.4 compared to 83 ± 13 ng/100 ml under treatment ($P < 0.05$).

Study with Lugol's solution (Fig. 3). Inorganic iodine induced a rapid fall in serum T_3 and, to a minor extent, in serum T_4 and rT_3 . Serum T_3 remained low for the first 6 days. Later its concentration tended to increase and after 28 days of treatment, exceeded even the initial serum concentration. There was no significant difference between the control and experimental period.

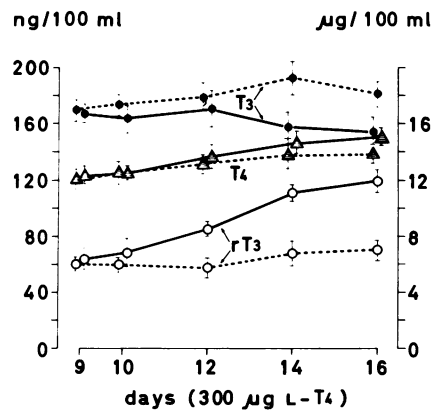


FIGURE 4 Effect of 400 mg amiodarone on thyroid hormone serum concentrations in T_4 -substituted subjects ($300 \mu g$ $L-T_4$ daily). The solid curves represent the amiodarone-treated group, the interrupted ones the control group treated with $300 \mu g$ T_4 only. For symbols see Fig. 1. Notice that serum T_3 , T_4 , and rT_3 continued to increase until day 16 under T_4 treatment only, an indication that equilibrium was not attained.

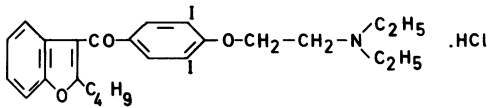


FIGURE 5 The structure of amiodarone: 2-*n*-butyl-3-(4'-diethylaminoethoxy-3'5'-diiodobenzoyl)-benzofurane.

The serum hormone levels of the amiodarone study and the one with Lugol's solution were compared by one-way analysis of variance. During the control period, there was no significant difference between the two experimental groups. During the treatment, serum T_3 levels were not statistically different in the two groups, while serum T_4 and rT_3 values of the group treated with amiodarone were significantly increased ($P < 0.01$). On the 28th day of amiodarone treatment, mean serum rT_3 concentration was 118 ng/100 ml and serum T_4 was 3 $\mu\text{g}/100$ ml above the corresponding mean serum hormone levels during treatment with Lugol's solution.

Study with combined L- T_4 and amiodarone treatment. The short-term pretreatment with L- T_4 did not allow attainment of equilibrium. The hormone measurements had to be compared to the control group of six subjects substituted with T_4 only. The results of both groups are shown in Fig. 4. Amiodarone (solid lines) had the most marked influence on serum rT_3 , which increased rapidly and to a similar extent, as with amiodarone alone (55 ± 7 ng/100 ml compared to 51 ± 10 ng/100 ml with amiodarone alone, see Fig. 1). The comparison by one-way analysis of variance with the serum rT_3 in the control group showed a significant difference ($P < 0.05$). Serum T_3 levels had a slight but nonsignificant tendency to fall during amiodarone treatment, yet the comparison of these serum T_3 levels with the control group showed them to be very significantly lower ($P < 0.01$). For serum T_4 , on the other hand, the increase with amiodarone treatment was only slightly greater than in the control group ($P = 0.1$). On the 6th day of amiodarone treatment, the mean serum T_4 was 1.2 $\mu\text{g}/100$ ml above, serum T_3 28 ng/100 ml below, and serum rT_3 49 ng/100 ml above the control group. Serum TSH remained unmeasurable throughout the 2 h after the TRH injection.

DISCUSSION

Serum T_3 and rT_3 can vary independently from the serum T_4 concentration. In particular, low serum T_3 and increased serum rT_3 concentrations have been encountered in the newborn, in acute and chronic diseases, and during fasting (11-14). Amiodarone induces changes in serum hormone concentrations similar to those during fasting. It is unlikely that these changes are the result of competition between the drug and the thyroid hormones for serum protein-binding sites. In such cases, free hormone fraction would increase while

the total serum hormone concentration would decrease. In the present study, serum T_3 decreased, and the free fraction of T_3 also had a tendency to decrease. The latter finding excludes an effect of competition between amiodarone and T_3 for thyroxine-binding globulin. Furthermore, serum T_4 and rT_3 , both of which bind to thyroxine-binding globulin, increased considerably (15). In addition, any in vivo or in vitro interference of the drug or one of its metabolites in the radioimmunoassays was excluded.

We therefore investigated whether the drug could interfere in thyroid hormone metabolism. For this purpose, two studies were performed. In the first, amiodarone was given for 28 days to euthyroid subjects. In the second, thyroidal secretion was completely suppressed with a slightly supraphysiological dose of T_4 (300 $\mu\text{g}/\text{day}$). In the first study the most marked changes occurred during the initial 6 days of treatment. The risk of side effects was therefore reduced in the second study by giving amiodarone from the 10th to the 16th day of L- T_4 treatment. The control studies consisted of 28 days of treatment with Lugol's solution and 16 days of L- T_4 treatment.

The most remarkable effect of amiodarone was the rapid increase in serum rT_3 , practically identical in the euthyroid and in the T_4 -substituted subjects. For serum T_3 there was an apparent discrepancy between the two groups, as in the T_4 -substituted subjects T_3 did not decrease. Nevertheless, in the T_4 -substituted group, amiodarone inhibited the increase of serum T_3 seen in the respective control group. The difference in serum T_3 between the euthyroid and the T_4 -substituted subjects treated with amiodarone was therefore minor. It can be explained by the excess iodide freed during the metabolism of the drug. Iodide is known to block thyroidal secretion (16). The decrease of serum T_3 and to a minor extent of serum T_4 during treatment with Lugol's solution are in keeping with this concept. Hence, it is likely that the serum hormone changes in the euthyroid subjects treated with amiodarone depended on two factors: iodide and the drug itself. The amiodarone effect can therefore best be seen in the T_4 -substituted group. These experiments suggest that the production of serum T_3 decreased while the metabolism of serum T_4 was diverted to rT_3 . In other words, it is postulated that the conversion of T_4 to T_3 can be blocked partly by amiodarone. Other substances have been postulated to interfere at this step, for instance propylthiouracil, thyroid hormone analogues, and possibly butyl-4-hydroxy-3,5-diiodobenzoate (17/20). Therefore, it is interesting to compare the structure of amiodarone with T_4 , to which it has some similarities (Fig. 5). Amiodarone could compete with T_4 for the deiodinative site, or other mechanisms may be involved, such as changes in clear-

ance rates and distribution space of T_4 and its metabolites.

Amiodarone treatment also caused changes in serum TSH concentrations. As in earlier experiments with iodine treatment, there was a transient rise in serum TSH, and the response of TSH to TRH was increased when compared to a control period (21). Nevertheless, there was one difference between these experiments and the present study: the response of T_3 in the TRH test was previously observed to be inhibited by iodine treatment, while in the present study serum T_3 increased nearly twice as much as in the control TRH test, excluding any important blocking effect of this drug on thyroid hormone secretion. The pituitary, on the other hand, sensed the decrease in serum T_3 and responded differently. The end-organ response to T_3 and also to T_4 may therefore be of crucial importance.

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