Effect of amiodarone on serum triiodothyronine, reverse triiodothyronine, thyroxin, and thyrotropin. A drug influencing peripheral metabolism of thyroid hormones.

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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 mug L-thyroxine (T4) for 16 days; from the 10th to the 16th day, 400 mg of amiodarone was added; and (d) five euthyroid subjects received 300 mug L-T4 for 16 days. The changes in serum thyroid-stimulating hormone (TSH), serum total T4, 3,5,3'-triiodothyronine (T3), free T3, and 3,5',3'-triiodothyronine (reverse T3, rT3) 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 T3 (28+/-5.1 ng/100 ml, mean+/-SEM, P less than 0.05) and 82.7+/-9.3 ng rT3/100 ml, P less than 0.01). The control study with an equal amount of inorganic iodine did not induce these opposite changes but slightly lowered serum rT3, T3, and T4. In the third study, serum rT3 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 […]

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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'-diethy laminoethoxy-3',5'-diiodobenzoyl)-benzofuran e (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 were treated, for the same period of time, 150 mg of iodine in the form of Lugol's solution; (c) five subjects received 300 µg L-thyroxine (T₄) for 16 days; from the 10th to the 16th day, 400 mg of amiodarone was added; and (d) five euthyroid subjects received 300 µg L-T₄ for 16 days. The changes in serum thyroid-stimulating hormone (TSH), serum total T₃, 3,5,3'-triiodothyronine (T₃), free T₄, and 3,5,3'-triiodothyronine (reverse T₃; rT₃) 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 T₃ (28±5.1 ng/100 ml, mean ± SEM, P < 0.05), whereas serum T₄ and rT₃ increased (1.4±0.4 µg T₄/100 ml, NS and 82.7±9.3 ng rT₃/100 ml, P < 0.01). The control study with an equal amount of inorganic iodine did not induce these opposite changes but slightly lowered serum rT₃, T₃, and T₄. In the third study, serum rT₃ 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 T₄ to T₃ and inducing a preferential production of rT₃.

Amiodarone also increased the response of TSH to TRH. The maximal increment of serum TSH above base line was 32±4.5 µU/ml under treatment and 20±3 µU/ml before treatment (P < 0.01). During this test, the serum T₄ 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'-diethy laminoethoxy-3',5'-diiodobenzoyl)-benzofuran e (amiodarone)³ 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 (T₄) was studied, with serum 3,5,3'-triiodothyronine (T₃) and 3,3',5'-triiodothyronine (reverse T₃; rT₃) as the peripheral products of T₄ metabolism. It was found that this drug reduced serum T₄ and increased serum rT₃ and T₃. To prove that its effect was peripheral, the study was repeated in T₄-treated subjects.

Methods

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

³Cordarone, Labaz Inc., Brussels, Belgium.

Abbreviations used in this paper: rT₃, reverse T₃ (3,5,3'-triiodothyronine); T₃, 3,5,3'-triiodothyronine; T₄, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

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thyroid disease was negative. The thyroid glands were inspected by palpation, and in the amiodarone study thyroid scans with $^{99m}$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$_3$ 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$_3$ and T$_4$ were performed according to Mitsuma et al. (3) in a slightly modified form (4, 5). T$_3$ 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$_3$ was measured according to Roberts and Nicolaí (8). The normal values (mean±2 SD) for serum T$_3$ were 8.2±3.9 µg/100 ml, for T$_4$, 165±46 ng/100 ml, and for T$_4$, 45±20 ng/100 ml. The fraction of serum free T$_3$ was determined by equilibrium dialysis, the normal value being 0.169±0.11% (9). The normal range for serum TSH was from <0.5 to 6 µU/ml.

**Statistical analysis.** The results were expressed as the mean±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 µg/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 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 µg 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.

**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$_4$ 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](image-url)
were measured 11 days before and 2 and 28 days after commencement of treatment. They were 0.13±0.06%, 0.136±0.1%, and 0.136±0.07%, respectively (NS). The converse changes were seen with serum rTs. Its serum concentration increased immediately with amiodarone treatment. 28 days later, the serum rTs 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 T4 concentration dropped during the first days of treatment and increased slightly thereafter. By the 28th day the increase was 1.4±0.4 ng/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.

* Values significantly elevated (P < 0.05).

Figures 2 and 3. Figure 2 shows that the 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 illustrates the 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 (A max TSH) was 32±4.5 μU/ml, compared to 20±3 μU/ml during the control phase. The increased TSH secretion resulted also in a greater rise of serum T4. The mean absolute increase in T4 (A max T4) 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 T4 and, to a minor extent, in serum T3 and rT3. Serum T3 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.

Table I

<table>
<thead>
<tr>
<th>Basal Serum TSH during Amiodarone Treatment</th>
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<tr>
<td>Before treatment Day of treatment</td>
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<tr>
<td>Mean</td>
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<td>4.4</td>
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<td>SEM</td>
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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 T3 levels were not statistically different in the two groups, while serum T4 and rT3 values of the group treated with amiodarone were significantly increased (P < 0.01). On the 28th day of amiodarone treatment, mean serum rT3 concentration was 118 ng/100 ml and serum T4 was 3 μg/100 ml above the corresponding mean serum hormone levels during treatment with Lugol's solution.

**Study with combined L-T4 and amiodarone treatment.** The short-term pretreatment with L-T4 did not allow attainment of equilibrium. The hormone measurements had to be compared to the control group of six subjects substituted with T4 only. The results of both groups are shown in Fig. 4. Amiodarone (solid lines) had the most marked influence on serum rT3, 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 rT3 in the control group showed a significant difference (P < 0.05). Serum T3 levels had a slight but nonsignificant tendency to fall during amiodarone treatment, yet the comparison of these serum T3 levels with the control group showed them to be very significantly lower (P < 0.01). For serum T4, 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 T4 was 1.2 μg/100 ml above, serum T4 28 ng/100 ml below, and serum rT3 49 ng/100 ml above the control group. Serum TSH remained unmeasurable throughout the 2 h after the TRH injection.

**DISCUSSION**

Serum T3 and rT3 can vary independently from the serum T4 concentration. In particular, low serum T3 and increased serum rT3 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 T4 decreased, and the free fraction of T4 also had a tendency to decrease. The latter finding excludes an effect of competition between amiodarone and T4 for thyrroxine-binding globulin. Furthermore, serum T3 and rT3, 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 T3 (300 μg/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-T4 treatment. The control studies consisted of 28 days of treatment with Lugol's solution and 16 days of L-T4 treatment.

The most remarkable effect of amiodarone was the rapid increase in serum rT3, practically identical in the euthyroid and in the T3-substituted subjects. For serum T4 there was an apparent discrepancy between the two groups, as in the T3-substituted subjects T4 did not decrease. Nevertheless, in the T3-substituted group, amiodarone inhibited the increase of serum T3 seen in the respective control group. The difference in serum T3 between the euthyroid and the T3-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 T4 and to a minor extent of serum T3 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 T3-substituted group. These experiments suggest that the production of serum T3 decreased while the metabolism of serum T4 was diverted to rT3. In other words, it is postulated that the conversion of T4 to T3 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 T3, to which it has some similarities (Fig. 5). Amiodarone could compete with T3 for the deiodinative site, or other mechanisms may be involved, such as changes in clear-
ance rates and distribution space of T₃ 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 T₃ in the TRH test was previously observed to be inhibited by iodine treatment, while in the present study serum T₃ 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 T₃ and responded differently. The end-organ response to T₃ and also to T₄ may therefore be of crucial importance.

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