Sensitivity to Lithium in Treated Graves’ Disease: Effects on Serum T₄, T₃ and Reverse T₃¹,²

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ABSTRACT. Seven patients judged to be euthyroid following treatment of diffuse toxic goiter were studied to determine if they were susceptible to lithium induced hypothyroidism. Lithium carbonate was administered for 4-7 weeks in a dosage (900 mg/day) which maintained serum lithium levels between 0.5-1.0 mEq/l. Blood was obtained weekly for the determination of serum 3,5,3’-triiodothyronine (T₃), thyroxine (T₄), 3,3’,5’-triiodo-L-thyronine (reverse T₃, rT₃) and thyrotropin (TSH). Values observed during lithium therapy were compared to those obtained prior to, and approximately one week after discontinuing lithium. During the pretreatment period, mean (± SE) serum T₃, T₄, and rT₃ concentrations were 130 ± 21 ng/100 ml, 7.6 ± 0.4 /u.g/100 ml and 48 ± 8 ng/100 ml, respectively, and decreased during lithium administration with the lowest T₃, T₄ and reverse T₃ concentrations of 92 ± 8 ng/100 ml, 4.9 ± 0.6 /u.g/100 ml, and 33 ± 6 ng/100 ml, respectively, being reached between the fourth and sixth weeks of study. Thereafter, and in spite of continued treatment with lithium, values for serum concentrations of T₃, T₄, and rT₃ plateaued, or actually increased in 4, 6, and 5 subjects, respectively. Serum TSH concentrations remained 3.0 µU/ml or less throughout the study in 6 patients; 2 of these subjects had no TSH response to thyrotropin-releasing hormone (TRH), even though they had been euthyroid for 3 and 10 months.

These data suggest that patients euthyroid following treatment of diffuse toxic goiter display sensitivity to the antithyroid effects of lithium. Furthermore, these observations support the thesis that the inhibitory effects of lithium and iodine upon thyroid hormone synthesis or secretion may involve a similar mechanism of action since increased thyroidal iodine content may be a consequence of therapy with either agent. (J Clin Endocrinol Metab 43:606, 1976)

LITHIUM and iodine³ have been demonstrated to have antithyroid effects in hyperthyroid individuals. Both agents inhibit thyroid secretion and, as a result, produce a decrease in circulating levels of triiodothyronine (T₃) and thyroxine (T₄) (1–5). Euthyroid subjects are more resistant to the antithyroid effects of these ions, and hence only a small percentage of normal in-

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² Portions of this study have been presented at the 57th annual meeting of the American College of Physicians, Philadelphia, Pennsylvania, April, 1976.

³ Throughout this report the term iodine has been used interchangeably to represent either organic or inorganic iodine.
tion. The measurement of 3,3',5'-triiodo-L-thyronine (reverse T₃, rT₃) as well as T₃ and T₄ in the present group of patients was performed to help determine whether lithium was having a direct effect on thyroidal secretion or whether the drug was influencing the peripheral conversion or degradation of T₄ (13–16).

Materials and Methods

Seven patients (three men, four women; average age 37 years, range 27–43) who had been euthyroid for an average of eleven months following radioiodine (six patients) or antithyroid (patient 7) treatment of diffuse toxic goiter were studied (number of months euthyroid without medication: 1, 6; 2, 12; 3, 13; 4, 3; 5, 17; 6, 15; 7, 10). Initially, all patients were considered to be euthyroid based upon clinical evaluation, normal serum T₄, and normal radioiodine uptake by the thyroid gland. The thyroid glands of all patients were initially estimated to be less than 40 g. The study protocol was divided into a control period which lasted 1–3 days, a post-treatment period which lasted 1–7 days, and an experimental period which lasted 4–7 weeks. Patients 6 and 7 received lithium for 5 and 4 weeks, respectively; the remaining 5 patients (1, 2, 3, 4, 5) were administered lithium for 7 weeks. During the experimental period, 300 mg lithium carbonate was administered orally three times daily, a dose sufficient to maintain the serum lithium level between 0.50 mEq/l and 1.0 mEq/l. During the control and post-treatment periods, the patients received no medications. At approximately weekly intervals, blood was drawn between 0800 and 1000 h for the determination of serum thyrotrpin (TSH), T₃, T₄, and rT₃. After lithium had been discontinued, 500 μg thyrotropin-releasing hormone (TRH) was administered iv to six of the seven subjects (17).

Each hormone measurement for an individual patient was analyzed in a single assay after the termination of the study. Serum TSH was determined in duplicate by radioimmunoassay as previously described (normal range, <1–5 μU/ml) (17,18); serum T₃ was determined in triplicate by a modification of the method of Chopra et al. (19), utilizing antisera obtained from Dr. D. Mayes, Endocrine Sciences, Tarzana, California (normal range, 60–185 ng/100 ml); and serum T₄ was measured in duplicate by the RIA-MAT™ Circulating T₄ ¹²⁵I-Kit (Mallinkrodt Inc., St. Louis, Missouri; normal range, 4.5–12.0 μg/100 ml). Serum rT₃ was measured in duplicate by radioimmunoassay utilizing a rabbit antiserum directed against the L form of the hormone which had been kindly supplied by Dr. Hans Cahnmann, National Institutes of Health, Bethesda, Maryland. Serum was analyzed directly without extraction (20) by the addition of 300 μg 8-anilino-l-naphthalene sulfonic acid to each assay tube. This antiserum does not cross react with various thyroid hormone analogues including 1000 ng/100 ml T₃ and 20 μg/100 ml T₄. The intra-assay coefficient of variation throughout the standard curve is less than 3%. The normal range (mean ± 2 SD) in our laboratory is considered to be 36–84 ng/100 ml. Thyroglobulin and microsomal thyroid antibodies were measured by use of Sera-Tek Test Kits (Ames Co., Div. of Miles Lab., Inc., Elkhart, Indiana). This protocol was approved by the hospital research committee and prior informed consent was obtained from each patient.

Results

T₃ (see Fig. 1, Table 1)

The mean (±SE) T₃ level during the control period was 130 ± 21 ng/100 ml; during lithium administration, decreases in serum T₃ levels were observed in 4 or 5 of 7 patients. When serum T₃ levels were analyzed consecutively during each week of lithium administration, the mean (±SE) serum T₃ nadir concentration of 92 ± 8 ng/100 ml was achieved during the sixth week of lithium administration. Following the discontinuation of lithium, the mean (±SE) T₃ level increased to 154 ± 15 ng/100 ml.

T₄

The mean (±SE) T₄ control level was 7.6 ± 0.4 μg/100 ml. Although the decrease in patient 6 was slight, all 7 subjects had decreases in their serum T₄ concentrations during the experimental period. The mean (±SE) T₄ nadir concentration of 4.9 ± 0.6 μg/100 ml was achieved during the fourth week of lithium administration. The mean
The control (±SE) $T_4$ level during the post-treatment period was 7.7 ± 0.4 µg/100 ml.

$rT_3$

The mean (±SE) $rT_3$ concentration was 48 ± 8 ng/100 ml during the control period and 5 of 7 patients had decreases in serum $rT_3$ during lithium administration. The mean (±SE) reverse T3 level reached its nadir (33 ± 6 ng/100 ml) during the fourth week of lithium administration and increased to 54 ± 4 ng/100 ml in the post-treatment period.

Despite the decreases in serum $T_3$, $T_4$, and $rT_3$, none of the patients had alterations in the size of their thyroid gland and all patients appeared to remain clinically euthyroid. Following the achievement of their lowest serum concentration, 4 patients (2, 3, 4, 7) had increases in serum $T_3$ levels, 6 patients (1, 2, 3, 4, 5, 6) had increases in serum $T_4$ levels, and 5 patients (1, 3, 4, 5, 7) had rises in serum $rT_3$ concentrations, in spite of continued lithium therapy and stable serum lithium levels.

TSH

Although $T_3$ and/or $T_4$ decreased during the experimental period, little change was observed in basal TSH levels. Serum TSH remained less than 1.25 µU/ml in 4 patients (1, 3, 4, 7), increased from 1.25 µU/ml in the control period to 2.4 µU/ml during the experimental period in patient 2, and from 2.5 µU/ml to 3.0 µU/ml in patient 6.
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| **Mean** | 7.6 | 6.3 | 5.8 | 5.0 | 4.9 | 5.1 | 5.0 | 6.0 | 7.7 |
| **SE**   | 0.4  | 0.7  | 0.4  | 0.4  | 0.6  | 0.9  | 0.6  | 0.6  | 0.4  |

### Thyroxine

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| **Mean** | 48 | 51 | 42 | 39 | 33 | 47 | 38 | 48 | 54 |
| **SE**   | 8  | 3  | 6  | 6  | 6  | 8  | 4  | 6  | 4  |

* Normal range, 60–185 ng/100 ml.
† Normal range, 4.5–12.0 μg/100 ml.
‡ Normal range, 36–84 ng/100 ml.
§ 1–3 days duration.
* 1–7 days duration.

TRH stimulation tests were performed in 5 of the 6 subjects in whom TSH levels remained 3.0 μU/ml or less throughout the study. Of these patients, three (1, 3, 6), had peak TSH levels following TRH administration of 5.3 μU/ml, 5.5 μU/ml, and 20.4 μU/ml, respectively, whereas two patients (4, 7) had serum TSH concentrations following TRH administration that did not rise above their baseline values of 1.5 μU/ml.

Although patient 5 fulfilled the initial criteria for inclusion into this study (i.e., normal serum T4, normal RAIU, and clinical euthyroidism), he was clearly atypical in several of his responses. Firstly, he consistently had lower serum T3, T4, and reverse T3 levels during the control period than during the first week of lithium administration. Subsequently, however, with continued lithium treatment, levels of each
of the iodothyronines gradually decreased. Secondly, this patient had baseline TSH concentrations which were initially slightly elevated (11.8 μU/ml) and subsequently increased to >40 μU/ml during lithium treatment, suggesting a pituitary feedback response to decreasing serum T4 and T3 levels. Although basal TSH concentration decreased to 16 μU/ml in the post-treatment period, the elevated basal levels and hyperresponse to TRH (peak TSH levels >40 μU/ml) indicate that this patient was either mildly hypothyroid or was being maintained both clinically and chemically euthyroid by virtue of endogenous TSH stimulation.

**Thyroid antibodies**

None of the 7 subjects had detectable thyroglobulin antibodies. However, microsomal antibody titers were as follows: 1, 1:409,600; 2, 1:400; 3, 1:25,600; 4, 1:100; 5, 1:1600; 6, 1:25,600; 7, negative.

**Discussion**

In the present study, patients rendered euthyroid following treatment of diffuse toxic goiter demonstrated sensitivity to the antithyroid effects of lithium, a finding similar to previous experiments employing iodine (11). These studies differ slightly, however, in the degree of decreases observed in the iodothyronines measured. In our study, lithium administration was associated with decreases in serum T3 and T4 concentrations of 30–40%, whereas iodine induced 70–80% decreases in levels of these thyroid hormones (11). Although these two agents are not necessarily comparable, the disparity in effect may also relate to relative differences in dose and duration of administration; the question of relative efficacy of these substances might be settled by assessment of the effect on thyroid hormone levels of the separate administration of lithium and iodine to the same group of patients euthyroid following treatment of hyperthyroidism.

In contrast to the observed effects of lithium in our patients, with a few possible exceptions (21,22), probably related to higher doses of lithium (21), euthyroid individuals do not generally demonstrate alterations in serum T3, T4, and TSH concentrations when administered lithium in comparable doses for similar intervals of time (3,6–10). A determination of whether the subjects reported herein are truly sensitive to lithium depends in part upon the demonstration that normal subjects are not similarly sensitive. Although a control group of subjects was not examined in our study, the literature affords adequate documentation of the responses of normal subjects to lithium. The administration of lithium for 3 weeks to eight euthyroid volunteers (7) or for 16 weeks to four patients (10) did not result in significant alterations of basal concentrations of serum T3, T4, or TSH, although TSH responses to TRH were increased in both groups. Two of an additional 17 patients studied by McLarty et al. (10) became hypothyroid after long term lithium therapy (16 and 17 months). The dose of lithium in the study by Lauridsen et al. (7) was 600–900 mg daily whereas the dose of lithium utilized in the study by McLarty et al. (10) ranged between 750 and 2750 mg daily.

Burrow et al. (9) also observed no significant differences in mean TSH, T4, and protein bound iodine during 3–4 weeks of lithium administration in a group of 9 patients. During more chronic drug therapy, Lindstedt et al. (8) noted that 8 of 334 patients had elevated TSH concentrations. Emerson et al. (6) examined thyroid function prospectively in 27 patients and separately evaluated an additional 228 patients who had already received lithium for varying lengths of time. In the prospective study, serum T4 concentrations did not decrease significantly but the mean serum TSH values increased from 3.3 to 5.3 μU/ml within the first 3 months of study. In the 228 patients already receiving lithium, the highest observed TSH concentrations were averaged; this mean TSH was found to be more elevated than
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that in the control groups. Approximately 30% of these patients had an elevated TSH concentration measured sometime during treatment, and it appears that approximately 15% of 57 subjects had an elevated TSH value when studied during the first 1-3 months of therapy. Although the mean T4 concentration in the 228 subjects who were analyzed while receiving lithium was only slightly lower than in the control groups, it is difficult to ascertain what percentage of patients had decreased serum T4 levels during the first 3 months of therapy. The duration of this interval is important in order to permit comparison of these data to the patients in the present report who received lithium for only 4 to 7 weeks. In contrast to the occasional occurrence of a decreased T4 or increased TSH in volunteers and psychiatric patients (3,6-10), the subjects in the present study consistently displayed decreases in each of their serum thyroid hormone concentrations during lithium administration. Serum T2 levels decreased in all 7 patients and serum T3 and rT3 concentrations decreased in 4 or 5 of 7 subjects.

Although the mechanism underlying the observed susceptibility to the antithyroid effects of lithium is unknown, it can be speculated that intrathyroidal iodine content may be important in this regard. Lithium decreases hormonal synthesis and thyroidal secretion, but does not appear to affect iodine uptake (1,2,23,24). Consequently, intrathyroidal iodine content may actually increase during lithium administration (24), and excessive quantities of intrathyroidal iodine may inhibit both thyroid hormone synthesis and release (5,25). The normal thyroid gland, however, will gradually overcome the inhibitory effects of iodine upon thyroid hormone synthesis and restore normal synthetic ability despite intrathyroidal iodine concentrations that remain elevated (25,26). Patients with diffuse toxic goiter may be unable to re-establish normal autoregulation of thyroidal iodine economy, possibly due to a defect in organic binding (11). As a result, there may be enhanced sensitivity for the development of hypothyroidism during treatment with either lithium or iodine. Sensitivity to these agents may exist regardless of the method of treatment that had been previously employed for the hyperthyroidism, although radioiodine treated patients appear to be especially susceptible (11). Verification of this speculation regarding the mechanism of sensitivity, however, would require further knowledge concerning the percentage and interconversion of inorganic and organic iodine which occurs within the thyroid gland of normal individuals as well as in subjects treated with lithium and iodine. A recent study by Clark et al. (27) suggests that sensitivity to the antithyroid effects of iodine may also occur in hemithyroidectomized patients; it would be of additional interest to study the effect of administering lithium to such patients.

Slight decreases in serum T3 and T4 concentrations, increases in serum TSH, and enhanced TSH response to TRH have been demonstrated during short term iodine and lithium administration to euthyroid individuals (7,10,27-29). In the present study, however, decreases in serum T3 and T4, as well as TRH administration, generally produced slight or negligible increases in serum TSH concentrations. These observations are consistent with the previous demonstration by others that an abnormal pituitary-thyroid axis may persist weeks or months after a normal, euthyroid goitrous, or hypothyroid individual has discontinued exogenous thyroid hormone administration or after a previously thyrotoxic patient has been rendered euthyroid (30-36). Moreover, these findings suggest that alterations in the hypothalamic-pituitary-thyroid axis may play a role in the sensitivity of treated hyperthyroid patients to the antithyroid effects of lithium.

Following the achievement of their lowest serum T3, T4, and rT3 concentrations, most patients in the present study had a rise in these hormones despite the continuation of lithium administration. Remarkably, these
increases also occurred in two patients (4 and 7) in whom serum TSH levels remained less than 1.5 μU/ml throughout the entire study period as well as following TRH administration. These data suggest that measurable rises in TSH concentration were not required in these patients for the thyroid gland to escape from the inhibitory effects of lithium on hormone synthesis and release, an observation which is consistent with previous studies concerning escape from iodine blockade in both animals (26) and man (37).

In contrast to other situations in which reverse T3 and T3 concentrations have been observed to vary reciprocally (13–16), lithium administration in the present study was associated with serum rT3, T3, and T4 levels which were altered in the same direction. These effects of lithium could be due to either direct inhibition of thyroidal release of T3, T4, and rT3, or to alterations in the metabolic clearance rates of these hormones, or, conceivably, could be related to both factors. For example, lithium might decrease thyroidal secretion of T4 as well as inhibit the 3 and 3' deiodinase enzyme systems so that both T3 and rT3 would decrease. Because only a limited number of studies concerning production, conversion, and secretion rates of rT3 have been performed (16,38) it is not possible, at the present time, to select any single explanation. Moreover, the mechanism of action of lithium in the present group of patients with treated Graves' disease may not apply to all of the effects of the drug on thyroid function in normal individuals or those with thyrotoxicosis. Nevertheless, it appears that lithium is not altering the peripheral conversion of T4 to T3 and rT3 in a manner similar to that observed during fasting (13) or corticosteroid therapy (14).

4 If lithium were decreasing serum T3, T4, and reverse T3 mainly by altering their affinity to their respective circulating binding proteins, increases in the resin T3 uptake test would be expected. Since this did not occur in the present study, a lithium-induced effect on affinity or binding protein concentrations seems unlikely.

Acknowledgments

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