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The feasibility of low-dose oral lithium therapy and its effect on thyroidal radioiodine uptake, retention, and hormonal parameters in various subcategories of hyperthyroid patients: a pilot study

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Background Radioactive iodine (^{131}I) (RAI) is used widely for the treatment of hyperthyroidism either as a first-line treatment or following relapse after antithyroid drug treatment. Intrathyroidal retention of RAI is considered an important determinant of its effectiveness, which is believed to be prolonged by lithium.

Aims and objectives To study the impact of low-dose oral lithium therapy on RAI uptake and retention parameters in different subgroups of hyperthyroidism patients, and thus explore its potential role in enhancing the therapeutic efficacy of RAI in these groups of patients.

Materials and methods A total of 28 patients (age range = 18–70 years) who were being considered for RAI therapy were included in this prospective pilot study. The patients were divided into two groups: (i) those who had not received any RAI therapy before were included in 'group I' ($n = 22$), whereas (ii) 'group II' ($n = 6$) included patients who were found to be persistently hyperthyroid on biochemical and clinical follow-up despite previous RAI therapy for hyperthyroidism. Patients in group I were further divided into four subgroups on the basis of the underlying etiopathology: (a) subgroup Ia – diffuse toxic goiter ($n = 15$), (b) subgroup Ib – autonomous functioning module ($n = 2$), (c) subgroup Ic – toxic multinodular goiter ($n = 4$), and (d) subgroup Id – nontoxic multinodular goiter ($n = 1$) on the basis of scintigraphic and clinical findings. All patients first underwent 25 μCi ^{131}I uptake estimation at 2, 24, and 48 h and values thus obtained were considered the baseline for further evaluation. After biochemical assessment of normal renal and liver functions, patients received 900 mg lithium per day in three divided doses orally, and on the fourth day after starting tab lithium, the serum lithium level was estimated with continued lithium administration. On the fifth, sixth, and seventh day, patients underwent lithium-primed 25 μCi ^{131}I uptake estimation at 2, 24, and 48 h. Retention index (RI) was calculated using the formula [RI = (48 h uptake − 24 h uptake)/24 h uptake × 100]. A day after completion of uptake study, that is, on the third day from diagnostic (25 μCi ^{131}I) RAI administration, patients received a fixed 5 mCi therapeutic RAI dose after their suitability for the same was ascertained using clinical, biochemical, and scintigraphic findings as the criteria. Lithium administration was stopped 5 days after therapy.

Results Lithium priming resulted in a significantly reduced serum FT4 level in subgroup Ia (diffuse goiter) of group I. Similarly, lithium priming resulted in a statistically significant increase in the radioiodine RI in subgroup Ia. Lithium priming resulted in increased retention of radioiodine and reduced serum FT4 level in the rest of the study population also, but the difference was not statistically significant (likely because of fewer patients in these subgroups). The low-dose lithium priming regimen used in the present study was found to be feasible and safe. The mean serum lithium concentration was 0.6 mEq/l with the dose protocol administered and hence was considered safe. Only one patient had achieved a level of 1.5 mEq/l, without any obvious side effects, and it was clinically uneventful. One patient experienced headache necessitating dose reduction.

Conclusion The results of this study, carried out in different groups of patients with hyperthyroidism, suggested that a short course of lithium is safe and could be beneficial for hyperthyroid patients considered for RAI therapy as it increased the RAI retention in thyroid, and thus had the potential to increase the effect of RAI therapy. Alternatively, it is proposed that lithium priming could help reduce the dose of RAI administered without compromising on therapeutic efficacy, with possible potential implications for cost reduction, radiation safety precautions, and lowered radiation dose to nontarget organs. *Nucl Med Commun* 37:74–78

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Introduction

Radioactive iodine (RAI) is used widely for the treatment of Graves' disease either as a first-line treatment or when hyperthyroidism relapses after a course of antithyroid drug treatment [1–4]. The effectiveness of radioiodine depends on several factors, including goiter size, 24 h

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thyroidal radioactive iodine uptake (RAIU), previous treatment with antithyroid drugs, and the rate of release of radioiodine after incorporation into thyroglobulin [5–7]. Release of organic iodine from the thyroid gland is blocked by iodine, but it is not used as an adjuvant to radioiodine because it reduces thyroidal uptake and recycling of radioiodine [8]. Lithium blocks the release of organic iodine and thyroid hormone from the thyroid gland without affecting thyroidal RAIU [5–7]. These effects are mediated either through potentiating an iodide-induced block of binding and hormone release [9, 10] or through inhibition of adenylate cyclase activity and blockage of cyclic AMP-mediated translocation of thyroid hormones [11]. The latter effect, which is probably responsible for the inhibition of hormone release, appears to be caused by the stabilization of thyroid cell microtubules promoted by lithium [12]. Accordingly, its use is postulated to increase the retention of iodine-131 (^{131}I) in the thyroid gland and thus increases the dose of radiation to the thyroid and conceivably reduces the dose required to achieve the therapeutic goal. More data are needed to support this approach for routine clinical use. The present study in subgroups of hyperthyroid patients represents an endeavor in this direction.

Materials and methods

Twenty-eight patients (age range = 18–70 years), most of whom were clinically, biochemically, and scintigraphically diagnosed as hyperthyroid and who would benefit from RAI therapy, were included in the study. The study was approved by the Institutional Medical Ethics Committee and written consent was obtained from all patients before recruiting each patient in the study protocol.

These patients were divided into two groups: (a) group I included patients who had not received RAI therapy before ($n = 22$). These patients were further subcategorized on the basis of underlying etiopathology and scintigraphic findings, that is, autonomous functioning nodule (subgroup Ia), diffuse toxic goiter (subgroup Ib), toxic multinodular goiter (MNG) (subgroup Ic), and nontoxic MNG (subgroup Id), and included 2, 15, 4, and 1 patient, respectively. There was only one patient with nontoxic MNG, who was being considered for ^{131}I therapy in view of refusal to undergo surgery. Group II included patients ($n = 6$) found to be persistently hyperthyroid on biochemical follow-up despite one dose of RAI therapy.

Patient preparation

The standard patient preparation methodology was followed. As per the SNMI procedure guidelines for thyroid uptake measurement version 3, September 2006, patients were asked to stop/avoid antithyroid drugs and other iodine-containing medications/procedures known to interfere with RAIU measurements, that is, antithyroid drugs should be withheld for 2–4 days, iodinated contrast for 2–4 weeks, and amiodarone for 6 months. Patients were asked to have fasted for a minimum 2 h before the administration of the capsule.

Study design

Two capsules, each containing 25 μCi RAI, were kept in a neck phantom separately and were counted using a thyroid uptake probe. The counts were obtained at a standard distance of 30 cm from the phantom. Two readings of each capsule were acquired for 100 s each and the average of two readings was then expressed as counts per minute (cpm). If the average count of two capsules was within ± 10%, then the first capsule was administered to the patient and he/she was asked to swallow it with plain water. The second capsule was kept in the neck phantom and was labeled as a 'standard capsule'.

After administration of the capsule, the patient's thyroid and thigh counts were taken using a thyroid uptake probe at 2, 24, and 48 h at the same distance and for the same time and expressed as cpm. Patients' thigh counts were used to correct for nonthyroidal blood pool activity.

The source was kept inside the lucite thyroid phantom and positioned at 30 cm from the detector (isoresponse distance) and counts were taken for the same time after each patient's readings, that is, at 2, 24, and 48 h, and reading was expressed in standard capsule cpm.

Percentage uptake was calculated using the following formula:

$$\text{Percentage uptake} = [\text{Thyroid counts(cpm)} - \text{thigh counts(cpm)}] \times 100.$$

Standard capsule counts (cpm)

The values thus obtained were considered the baseline for prospective evaluation.

Patients were again placed on maintenance-dose antithyroidal medications for 1 month. After stopping antithyroid medications and biochemically determining normal renal and liver functions, patients received oral lithium 300 mg three times a day for 12 days, and on the fourth day after starting the lithium treatment, lithium levels in serum were estimated with continued administration of lithium. On the fifth, sixth, and seventh day, patients underwent lithium-primed 25 μCi ^{131}I uptake estimation at 2, 24, and 48 h similar to the baseline study.

The retention index (RI) was calculated using the formula [RI = (48 h uptake − 24 h uptake)/24 h uptake × 100] for both baseline and lithium-primed studies separately.

A day after completion of the uptake study, that is, on the third day from diagnostic 25 μCi ^{131}I administration, patients received a fixed dose of 5 mCi therapeutic RAI

Table 1 Patient characteristics with respect to pathophysiology

Study group	Frequency	%
Group I		
Subgroup 1a: diffuse goiter	15	53.57
Subgroup 1b: AFTN	2	7.14
Subgroup 1c: toxic MNG	4	14.3
Subgroup 1d: nontoxic MNG	1	3.57
Group II	6	21.4
Total	28	100.0

AFTN, autonomous functioning thyroid nodule; MNG, multinodular goiter.

dose orally after their suitability for the same was ascertained using RAI uptake, scintigraphic findings, and biochemical thyroid function tests as per the standard norms. Lithium administration was stopped 5 days after administration of therapy dose.

Statistical analysis

The values were expressed as mean ± SD for quantitative variables and as percentage for qualitative variables, respectively. Data were recorded on a predesigned proforma and managed on an Excel spread sheet. Student's *t*-test was used to compare the difference in proportions in two groups. In this study, a P value of 0.05 was considered statistically significant. There was only one patient with nontoxic MNG (subgroup Id); hence, the mean value was not calculated for this subgroup.

Results

Twenty-eight patients [seven men (25%), 21 women (75%), age range = 18–70 years], most of whom were clinically, biochemically, and scintigraphically diagnosed as hyperthyroid and who would benefit from RAI therapy, were included in the study.

Twenty-two patients (78.6%) belonged to 'group I' and six patients (21.4%) belonged to 'group II' as per the criteria of classification described before. Patients in group I were further divided into four subgroups on the basis of the underlying etiopathology, scintigraphy, and clinical findings as: (a) subgroup Ia – diffuse toxic goiter ($n = 15$, 53.57%), (b) subgroup Ib – autonomous functioning nodule ($n = 2$, 7.14%), (c) subgroup Ic – toxic MNG ($n = 4$, 14.3%), and (d) subgroup Id – nontoxic MNG ($n = 1$, 3.57%) (Table 1).

In the subgroup Ia – diffuse goiter, the baseline mean serum free T4 (FT4) was 3.31 ± 1.44 (mean ± SD) and in the lithium-primed study, it was 2.76 ± 0.92, with a statistically significant difference ($P < 0.05$). The rest of the subgroups in group I and group II showed a decreased mean value, with no statistically significant difference in the serum FT4 level in the baseline and the lithium-primed study, possibly because of the small number of patients in each of these subgroups (Table 2). No statistically significant difference was observed in serum thyroid-stimulating hormone level in the baseline and the lithium-primed study in the study groups and subgroups (Table 3). Radioiodine uptake at 2, 24, and 48 h in the baseline and the lithium-primed study in all study groups and subgroups showed no statistically significant difference (Tables 4–6).

The RI (Table 7) showed a statistically significant difference in the baseline (−6.31 ± 7.95) and the lithium-primed study (−1.98 ± 6.85) in subgroup Ia – diffuse goiter of group I ($P < 0.05$). No statistically significant difference was noted in the baseline and the lithium-primed study in the rest of the study groups, again likely because of the smaller number of patients in each of these subgroups. The various parameters in the diffuse toxic group are summarized in Table 8.

Serum lithium concentrations

The mean serum lithium concentration was 0.6 mEq/l; only two patients (7.14%) had a serum lithium concentration greater than 1 mEq/l and among them, only one patient reached a 1.5 mEq/l serum lithium concentration. One patient had experienced headache necessitating dose reduction. The low-dose lithium priming regimen used in the present study was found to be feasible and safe.

Discussion

Thyrotoxicosis because of Graves's disease or nodular goiter can be treated with thionamides, RAI, or uncommonly thyroidectomy. Thionamides, although used frequently, are associated with a high relapse rate of hyperthyroidism on discontinuation. RAI treatment is used widely because it is easy to administer, increasingly available in several centers, and effective in most patients. However, hyperthyroidism recurs or persists in 15–18% of patients after RAI. Failure of RAI treatment may be influenced by several factors, including thionamide treatment, thyroid-stimulating hormone receptor antibody titers, large goiter, RAIU values, and their faster washout in some individuals. It is believed that lithium can significantly affect the intrathyroidal kinetics of iodine by reducing its release from the thyroid gland, thus increasing its retention [6,7,9–12]. The beneficial effects of lithium have been reported in cases of

Table 2 Effect of lithium priming on serum FT4 level in the study population

	Serum FT4 level (mean ± SD) (ng/dl)		
Study group	Baseline study	Lithium-primed study	*P* value
Group I			
Subgroup Ia (diffuse goiter)	3.31 ± 1.44	2.76 ± 0.92	0.030 (significant)
Subgroup Ib (AFTN)	1.5 ± 0.57	1.5 ± 0.57	0.80 (NS)
Subgroup Ic (toxic MNG)	2.84 ± 1.30	2.09 ± 0.63	0.63 (NS)
Group II	2.02 ± 0.83	1.68 ± 0.65	0.249 (NS)

AFTN, autonomous functioning thyroid nodule; FT4, free thyroxine; MNG, multinodular goiter; NS, not significant.

Table 3 Effect of lithium priming on serum TSH level in the study population

	Serum TSH level (mean ± SD) (μIU/ml)		
Study group	Baseline study	Lithium-primed study	*P* value
Group I			
Subgroup Ia (diffuse goiter)	0.12 ± 0.29	0.12 ± 0.29	0.901 (NS)
Subgroup Ib (AFTN)	0.05 ± 0.06	0.03 ± 0.03	0.736 (NS)
Subgroup Ic (toxic MNG)	0.05 ± 0.06	0.03 ± 0.03	0.736 (NS)
Group II	0.05 ± 0.06	0.07 ± 0.08	0.455 (NS)

AFTN, autonomous functioning thyroid nodule; MNG, multinodular goiter; NS, not significant; TSH, thyroid-stimulating hormone.

Table 4 Effect of lithium priming on 2 h radioiodine uptake

	2 h radioiodine uptake (mean ± SD) (%)		
Study group	Baseline study	Lithium-primed study	*P* value
Group I			
Subgroup Ia (diffuse goiter)	48.29 ± 17.97	45.64 ± 25.22	0.210 (NS)
Subgroup Ib (AFTN)	10.93 ± 0.73	11.21 ± 1.99	0.806 (NS)
Subgroup Ic (toxic MNG)	19.93 ± 18.91	18.60 ± 9.50	0.852 (NS)
Group II	30.46 ± 22.48	22.45 ± 15.02	0.154 (NS)

AFTN, autonomous functioning thyroid nodule; MNG, multinodular goiter; NS, not significant.

Table 5 Effect of lithium priming on 24 h radioiodine uptake in the study population

	24 h radioiodine uptake (mean ± SD) (%)		
Study group	Baseline study	Lithium-primed study	*P* value
Group I			
Subgroup Ia (diffuse goiter)	71.67 ± 11.84	69.67 ± 15.41	0.666 (NS)
Subgroup Ib (AFTN)	39.89 ± 1.98	48.72 ± 6.86	0.237 (NS)
Subgroup Ic (toxic MNG)	33.68 ± 21.78	45.08 ± 15.00	0.124 (NS)
Group II	43.16 ± 18.83	37.15 ± 15.70	0.241 (NS)

AFTN, autonomous functioning thyroid nodule; MNG, multinodular goiter; NS, not significant.

Table 6 Effect of lithium priming on 48 h radioiodine uptake in the study population

	48 h radioiodine uptake (mean ± SD) (%)		
Study group	Baseline study	Lithium-primed study	*P* value
Group I			
Subgroup Ia (Diffuse Goiter)	67.64 ± 14.10	68.01 ± 15.15	0.933 (NS)
Subgroup Ib (AFTN)	40.01 ± 4.71	49.69 ± 6.61	0.088 (NS)
Subgroup Ic (toxic MNG)	31.40 ± 19.03	48.25 ± 12.48	0.107 (NS)
Group II	40.96 ± 18.99	35.86 ± 14.23	1.181 (NS)

AFTN, autonomous functioning thyroid nodule; MNG, multinodular goiter; NS, not significant.

Table 7 Effect of lithium priming on radioiodine retention index in the study population

	Radioiodine retention index (mean ± SD)		
Study group	Baseline study	Lithium-primed study	*P* value
Group I			
Subgroup Ia (diffuse goiter)	−6.31 ± 7.95	−1.98 ± 6.85	0.030 (significant)
Subgroup Ib (AFTN)	0.13 ± 6.83	2.03 ± 0.79	0.784 (NS)
Subgroup Ic (toxic MNG)	0.13 ± 6.83	2.03 ± 0.79	0.784 (NS)
Group II	−5.38 ± 6.54	−2.02 ± 8.07	0.267 (NS)

AFTN, autonomous functioning thyroid nodule; MNG, multinodular goiter; NS, not significant.

radioiodine therapy of thyroid carcinoma [13–16]. However, in cases of hyperthyroidism, few such studies have been carried out. Turner *et al.* [17] were the first to suggest that lithium may be a useful adjunct therapy in the treatment of hyperthyroidism with radioiodine and documented an increased thyroidal retention of ^{131}I in their patients. Bogazzi *et al.* [18] showed that radioiodine plus lithium allows more rapid control of hyperthyroidism than radioiodine alone, although the two groups did not significantly differ at the end of the study in terms of the final outcome.

Our study also showed that lithium priming results in an increase in thyroid radioiodine retention in all study groups and can thus potentially increase the effectiveness of radioiodine treatment. The increase in thyroidal radioiodine retention achieved statistical significance in the diffuse goiter cohort of patients. Although it did not achieve statistical significance in the rest of the study population, one of the reasons for this could be the relatively smaller number of patients in the other subgroups. Further studies with a greater number of patients should be carried out to evaluate the effectiveness of lithium priming in increasing radioiodine retention in these subgroups of hyperthyroidism. Lithium priming can lead to changes in the effective half-life of iodine in the gland, thereby increasing its therapeutic effectiveness. The administration of lithium would increase the biologic half-life in the formula 1/effective half-life equals 1/biologic half-life +1/physical half-life. Hypothetically, an increase in the effective half-life of radioiodine in the gland should increase the dose of radiation to the target tissue and conceivably reduce the dose required to achieve the therapeutic goal.

It is a routine to stop antithyroid drugs 3–5 days before administering radioiodine treatment as they reduce the effectiveness of radioiodine treatment by blocking iodine organification. The increase in serum thyroid hormone was blunted in patients treated with lithium because of the inhibitory effect of lithium on the release of thyroid hormone in cell culture [7]. Our study also documented a reduction in the serum FT4 level in patients in the

Table 8 Summary of various study parameters in subgroup Ia – diffuse toxic goiter

Study parameters	Baseline study (mean ± SD)	Lithium-primed study (mean ± SD)	*P* value
Serum TSH level (μIU/ml)	0.12 ± 0.29	0.12 ± 0.29	0.901 (NS)
Serum FT4 level (ng/dl)	3.31 ± 1.44	2.76 ± 0.92	0.030 (significant)
Radioiodine uptake at 2 h (%)	48.29 ± 17.97	45.64 ± 25.22	0.210 (NS)
Radioiodine uptake at 24 h (%)	71.67 ± 11.84	69.67 ± 15.41	0.666 (NS)
Radioiodine uptake at 48 h (%)	67.64 ± 14.10	68.01 ± 15.15	0.933 (NS)
Retention index	−6.31 ± 7.95	−1.98 ± 6.85	0.030 (significant)

FT4, free thyroxine; NS, not significant; TSH, thyroid-stimulating hormone.

lithium priming study compared with the baseline study (while they were off antithyroid medication). The lithium priming resulted in significantly reduced serum FT4 levels compared with the baseline study in diffuse goiter patients. In the other group, statistical significance has not achieved because of the modest number of patients included. The reduction in thyroid hormone levels may be a valuable adjunct in this group of patients; many of these patients can become clinically symptomatic following withdrawal of antithyroid medications, which is necessary for an RAI uptake study and subsequent RAI therapy. This effect of lithium could be potentially valuable in the prevention of thyroid hormone surge after antithyroid drug withdrawal and this could be particularly valuable in elderly patients and those with pre-existing cardiac problems.

The mean serum lithium concentration was 0.6 mEq/l with the administered dose (900 mg/day in three divided doses) and hence could be considered safe. Side effects of short-term lithium therapy were almost absent. The overall results, therefore, suggest the potential adjunct value of lithium to radioiodine therapy for patients with hyperthyroidism, particularly those who have faster washout.

Conclusion

The results of this study, carried out in different groups of patients with hyperthyroidism, suggest that a short course of lithium is feasible and safe for hyperthyroid patients considered for RAI therapy. It increases the RAI retention in the thyroid and may thus help increase the effectiveness of RAI therapy. It is proposed that lithium priming would help to reduce the dose of RAI administered without compromising on therapeutic efficacy, with consequent implications in cost reduction, observation of radiation safety precautions, and lowered radiation dose to nontarget organs. Furthermore, the reduction in thyroid hormone levels may be a valuable adjunct in this group of patients, many of whom can become clinically symptomatic following withdrawal of antithyroid medications.

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Conflicts of interest

There are no conflicts of interest.

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