

Is low radioiodine uptake a contraindication to radioiodine therapy in patients with benign thyroid disease?

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Abstract

Background. Radioiodine therapy (¹³¹I) is a standard procedure in the treatment of hyperthyroidism in the course of Graves' disease or toxic nodules. However, the use of ¹³¹I in patients with low radioiodine uptake (RAIU) may be controversial.

Objectives. To determine the influence of lithium carbonate (Li) on iodine kinetics.

Materials and methods. Patients with hyperthyroidism and low RAIU (< 30%) were divided into 2 groups: a Li(–) group of 305 patients not receiving Li adjuvant therapy and a Li(+) group of 264 patients receiving adjuvant therapy. The serum concentrations of free triiodothyronine (fT3), free thyroxine (fT4) and thyroid stimulating hormone (TSH) were assessed at baseline, 24 h, 48 h, 72 h and 96 h, and 1, 6 and 12 months after ¹³¹I therapy. The RAIU was assessed after 5 h, 24 h, 48 h, 72 h, and 96 h.

Results. Levels of fT3 in the Li(+) group compared to the Li(–) group were significantly higher at baseline, lower after 48 h, 72 h, 96 h and 1 month, and did not differ significantly after 24 h, 6 months and 12 months. Levels of fT4 in the Li(+) group compared to the Li(–) group were significantly higher at baseline, lower after 24 h, 48 h, 72 h, 96 h and 1 month, and not differ significantly after 6 and 12 months. The RAIU in the hyperthyroidism Li(–) and Li(+) groups, respectively, was 11.9 ± 5.6% compared to 23.9 ± 10.1% (p < 0.001) after 5 h; 25.9 ± 8.3% compared to 40.5 ± 12.4% (p < 0.05) after 24 h; 7.8 ± 8.1% compared to 40.9 ± 13.7% (p < 0.05) after 48 h; 26.2 ± 10.2% compared to 39.5 ± 11.2% (p < 0.01) after 72 h; and 24.7 ± 7.1% compared to 37.4 ± 10.1% (p < 0.01) after 96 h.

Conclusions. Adjuvant therapy with Li in patients with hyperthyroidism caused a significant increase in RAIU and positive changes in the fT3 and fT4 profiles. The use of lithium carbonate prior to the inclusion of ¹³¹I in hyperthyroid patients with low RAIU should be considered.

Key words: hyperthyroidism, radioiodine therapy, lithium therapy, adjuvant lithium therapy, low radioiodine uptake

Background

Lithium carbonate (Li), which is a drug known for over 100 years, is successfully used in the treatment of depression. However, various studies have shown that it can cause the emergence of goiter and even hypothyroidism in the range of 3.4–52% of treated patients^{1–9} and, in extremely rare cases, hyperthyroidism.^{1,10,11} The mechanism of action of Li on thyroid function seems to be similar to that of iodine. It is believed that ionized lithium inhibits thyroglobulin proteolysis which, in turn, inhibits the release of thyroid hormones into the bloodstream and leads to a prolonged biological half-life of iodine.¹² Another mechanism involves inhibition of the conversion of free thyroxine (T4) to triiodothyronine (T3) by this drug.¹ Lithium carbonate has also been shown to reduce the concentration of thyroid hormone transporter proteins in the blood serum.^{1,13}

Radioiodine (¹³¹I) therapy is a very popular therapeutic method in patients with hyperthyroidism,^{14–18} especially in cases where antithyroid drugs (ATDs) have proved to be inefficient. The mechanism of action of ¹³¹I involves the total destruction of thyroid tissues, resulting in euthyroidism or hypothyroidism.^{19,20} However, it is very difficult to choose the right activity of ¹³¹I to achieve euthyroidism. Several studies have attempted to determine the optimal level to treat hyperthyroidism while avoiding the development of permanent hypothyroidism. Various ¹³¹I administration protocols are available, including low doses (80 MBq),^{14,21,22} various fixed doses (185 MBq, 370 MBq and 555 MBq),^{14,22–24} and doses calculated on the basis of thyroid size, radioactive iodine uptake (RAIU) or the turnover of ¹³¹I.^{14,24,25} However, our clinical experience has proven that hypothyroidism develops in approx. 80% of cases, which is not a significant problem for an experienced clinician, as it only requires the substitution of L-thyroxin.²⁶

The premise for using Li is that this compound leads to the inhibition of thyroglobulin proteolysis and release of thyroid hormones.¹ Therefore, it is assumed that the administered radioactive iodine accumulates in thyroid tissue to a higher degree, and thus ¹³¹I treatment is possible in patients with critically reduced RAIU at baseline. However, in the existing literature, there is relatively little data on the long-term results of the use of Li in patients with hyperthyroidism, especially those with a low radioiodine uptake (RAIU) after or during treatment with amiodarone,^{1,13,26,27} after coronary angiography, or in cases using iodine-containing contrast (e.g., eye drops or multivitamin preparations). Additionally, there are few publications related to the use of this type of therapy and the available publications have too short observation period or too few patients. Therefore, a method involving the administration of Li to hyperthyroid patients was introduced.²⁸

Objectives

The aim of this study was to demonstrate the usefulness and effectiveness of the administration of Li prior to the administration of ¹³¹I in patients with established hyperthyroidism for whom the reduced RAIU did not allow this type of treatment.

Materials and methods

Patients and study design

This retrospective study was conducted at the Department of Nuclear Medicine in Warszawa, Poland, from January 1, 2005, to December 31, 2016. The study was approved by the local ethics committee of the county of Warszawa. Our cohort comprised 569 consecutive patients with hyperthyroidism with reduced RAIU at baseline (<30%) and 78 patients with normal or elevated RAIU (comparison group) treated with ¹³¹I. Data were retrieved from the medical records of patients who were eligible for this study. Informed consent was obtained from all participants.

The patients were categorized into 3 following groups:

- group I (Li (-) group): patients with very low RAIU (<30%), with Graves' disease (GD), toxic nodular goiter (TNG) or iodine-induced toxic adenoma (TA) not treated with Li;
- group II (Li(+)) group): patients who received Li in order to increase RAIU (>30%), with GD, TNG or TA; and
- group III: the comparison group comprising hyperthyroid patients with GD treated with ¹³¹I with correct or elevated RAIU at baseline.

Among the included patients, low RAIU was caused by amiodarone therapy (n = 186, 32.7%), coronary angiography before the iodine uptake test (n = 281, 49.4%), iodine-containing eye drops (e.g., Iodoxouridine; n = 57, 10.0%), and multivitamin preparations containing iodine (n = 45, 7.9%).

The etiology of hyperthyroidism was established on the basis of clinical examination and history of the disease. The following diagnostic criteria for GD were applied: 1) biochemical hyperthyroidism (increased serum free T4 concentration and undetectable TSH) and diffuse goiter without nodules, with or without an isotopic scan; 2) the presence of the titer of the TSH receptor antibody (TRAb); and 3) symptoms of mild ophthalmopathy.

The TNG was defined as hyperthyroidism with the presence of nodular goiter on thyroid ultrasonography and ¹³¹I scintigraphy and, in the case of toxic adenoma, clinical or subclinical hyperthyroidism and the presence of hot nodules on scintigraphy.

The diagnosis of mild GO was defined based on the following criteria: goiter on thyroid ultrasound, mild proptosis or mild exophthalmos assessed using an exophthalmometer (<18 mm), and hormonal analyses showing suppressed TSH levels, as well as an increased concentration of free T4

(fT4) and free T3 (fT3) combined with positive autoantibodies in regard to the thyrotropin receptor (TSHR-Abs).

Patients with GD for whom long-term remission did not appear following ATDs treatment, and patients with persistent hyperthyroidism due to toxic multinodular goiter or single toxic adenoma, were administered ¹³¹I.

Study design

Using a thyroid uptake probe, we counted 2 capsules of 25 µCi ¹³¹I, each kept in a neck phantom. A standard distance of 30 cm was maintained from the phantom for the purpose of the count. We acquired 2 readings of 100 s for each capsule and, subsequently, expressed the average of the 2 readings as counts per minute (cpm). The first capsule was administered if the average count of the 2 capsules amounted to ±10%, and the patient was asked to swallow it with plain water. The 2nd capsule, labelled the 'standard capsule', was kept in the neck phantom. Following administration of this capsule, the patient's thyroid and thigh counts were measured using a thyroid uptake probe at 5 h, 24 h, 48 h, 72 h, and 96 h at the same distance and for the same time; the results were expressed as cpm. The patient's thigh counts were used for the correction of non-thyroidal blood pool activity. The source, which was kept inside the lucite thyroid phantom, was located 30 cm from the detector (isoresponse distance). Counts were taken at specific times after each patient's readings, namely at 5 h, 24 h, 48 h, 72 h, and 96 h, with the reading expressed in the standard capsule cpm. The following formula was used to calculate the percentage uptake:

$$\text{percentage uptake} = \frac{\text{thyroid counts [cpm]} - \text{thigh counts [cpm]}}{\text{thyroid counts [cpm]}} \times 100.$$

Iodine sensitivity tests were performed using a Siemens ZLC gamma camera (Siemens AG, Munich, Germany).

After performing RAIU and obtaining the activity of ¹³¹I, patients were scheduled to visit outpatient clinics at baseline (before radioiodine therapy (RIT)), and at 24 h, 48 h, 72 h and 96 h after the procedure, and after 1, 6 and 12 months during 1 year of follow-up after the initiation of RIT. The TSH, fT3, fT4, and thyroid autoantibodies were examined at every follow-up visit to the outpatient clinic.

Our study did not include patients with contraindications to Li, i.e., allergy to lithium, heart and kidney failure, hypothyroidism, uncontrolled arterial hypertension, water-electrolyte disorders, Addison's disease, or brain diseases with dementia.

Treatment

Antithyroid drug

The ATD therapy was discontinued in all patients before ¹³¹I therapy. Most patients (83%) did not receive ATD for 5–7 days before ¹³¹I treatment. The TD treatment was

discontinued in all other patients for a period of more than 7 days (7–25 days).

Lithium carbonate

Oral administration of adjuvant Li (GlaxoSmithKline Pharmaceuticals SA, Poznań, Poland) was recommended for patients with low RAIU. Patients were assigned to receive a daily oral average dose of 750 mg starting 3 days prior to ¹³¹I therapy and continuing for 7 days following the administration of ¹³¹I.

Radioiodine therapy

Radioactive iodine was administered as a single, standard, orally administered dose of 740 MBq (20 mCi) in patients with GD and TMG (with adjuvant lithium therapy (750 mg/day for 10 days) or without lithium). The administered activity of ¹³¹I in TA was 555 MBq (15 mCi), irrespective of adjuvant Li therapy.

L-thyroxine

In all patients with hypothyroidism (TSH > 4.5 mIU/L) after ¹³¹I therapy, L-thyroxin therapy was applied.

Assays

A Hitachi Cobas e601 chemiluminescent analyzer (Roche Diagnostics, Basel, Switzerland) was used to diagnose serum TSH levels (normal range: 0.27–4.2 µIU/mL) and to perform the hormonal assessments fT4, normal range: 11.5–21.5 pmol/L; fT3, normal range: 3.9–6.8 pmol/L). Determination of TSH concentrations was performed using third-generation assays (sensitivity: 0.005 µIU/mL). Second-generation antibodies (RIA-2 Dynotest TRAK human; BRAHMS Diagnostica GmbH, Berlin, Germany) were the radioimmunological method used to measure the titer of the antithyroid peroxidase autoantibody (TPO-Abs, reference range: <35 IU/mL), antithyroglobulin antibody (Tg-Abs, reference range: <115 IU/mL) and TSHR-Abs (reference range: <2 IU/L).

The serum level of Li was assayed by ion-selective lithium determination using a lithium electrode and an AVL 988-3 apparatus with automatic three-point calibration. This method consists of determining the difference in the potential of the lithium level between the standard and the sample. The selective potential between the 2 different concentrations of lithium ions was automatically measured. Using this method, the measurement limit for lithium is in the range of 0.1 ± 9.99 mmol/L and the sensitivity is 0.01 ± 0.02 mmol/L.

Sonography and scintigraphy

An Aloka SSD-500 (Aloka Ltd., Tokyo, Japan) ultrasound machine with a 7.5-MHz linear transducer was used

to perform ultrasonography of the thyroid. Ultrasound was also used to measure the thyroid volume. The ellipsoid model (width × length × thickness × 0.52 for each lobe) was used for the calculation.^{29,30}

In the case of patients with thyroid nodules, 150 MBq of ^{99m}Tc was intravenously administered and a thyroid scintiscan was performed (Nucline gamma camera; Mediso, Budapest, Hungary) 30 min later.

Statistical analyses

The thyroid hormone and TSH serum levels before and after administration of Li were assessed using Student's *t*-test for independent observations. Friedman's test was also used for statistical comparison of mean iodine

uptake measurements before and 5 h, 24 h, 48 h, 72 h, and 96 h after administration of Li. One-way analysis of variance (ANOVA) was used to establish if there was a statistically justified division of the analyzed data into subgroups of the various clinical forms of hyperthyroidism. Variance analysis was preceded by assessment of the compatibility of the variances of the hypothetical subgroups using Levene's test. The mean uptake of ¹³¹I before and after the administration of Li for particular groups at the determined measurement times was also compared using Student's *t*-test. Statistical analyses were performed using STATISTICA v. 12 software (StatSoft Inc. Tulsa, USA). The adopted level of statistical significance was $\alpha = 0.05$ and results were considered statistically significant when $p < \alpha$.

Table 1A. Baseline characteristic of the hyperthyroid patients (GD, TMG and TA) with reduced RAIU at baseline (<30%) according to the clinical diagnosis or the demographic, clinical and laboratory characteristics

Characteristic	GD (n = 284)		TMG (n = 231)		TA (n = 54)	
	Li(-)	Li(+)	Li(-)	Li(+)	Li(-)	Li(+)
Females (n, %)	121 (42.6)	107 (36.7)	79 (34.2)	74 (32.0)	22 (40.7)	9 (16.6)
Males (n, %)	23 (8.1)	33 (11.6)	41 (17.7)	37 (16.1)	19 (35.2)	4 (7.4)
Age of females, mean (range) [years]	49 (18–61)	45 (19–54)	51 (37–81)	54 (34–78)	54 (33–71)	55 (29–87)
Age of males, mean (range) [years]	43 (26–52)	47 (32–58)	59 (42–78)	62 (32–69)	52 (38–83)	56 (32–86)
Week of diagnosis	23	17	27	20	13	11
Mild ophthalmopathy yes (%) no (%)	96 (67) 48 (33)	102 (73) 38 (27)	0 (0) 120 (52)	0 (0) 111 (48)	0 (0) 41 (76)	0 (0) 13 (24)
TSH level [mIU/L] mean (SEM) range	0.0 (0.09) 0.0–0.012	0.0 (0.04) 0.0–0.05	0.13 (0.04) 0.1–0.21	0.1 (0.15) 0.01–0.20	0.15 (0.1) 0.14–0.23	0.18 (0.13) 0.1–0.22
Free T3 level [pmol/L] mean (SEM) range	9.6 (3.8) 3.9–12.7	8.7 (5.2) 4.6–11.2	6.6 (3.1) 3.3–8.4	4.3 (4.1) 3.6–9.6	4.3 (3.9) 3.6–5.7	3.9 (4.2) 4.1–6.2
Free T4 level [pmol/L] mean (SEM) range	29.1 (5.6) 25.0–39.7	32.2 (6.7) 24–45	26 (3.9) 35.5–32.5	23.91 (4.6) 22.4–32.3	22.9 (4.1) 18.9–25.9	21.71 (3.5) 20.4–27.1
TSHR-Abs titers [IU/L] mean (SEM) range	12.1 (5.6) 2.1–16.7	7.8 (4.8) 2.5–13.7	0.9 (0.6) 0.3–2.4	1.1 (0.5) 0.5–1.3	1.2 (0.5) 0.4–1.7	2.0 (0.6) 0.4–2.1
TPO-Abs titers [IU/mL] mean (SEM) range	332.6 (349.4) 79–451	249.4 (284.8) 134–456	64.5 (34.1) 19.0–71.3	56.1 (32.5) 31.0–81.7	52.2 (22.5) 19.5–49.3	45.7 (25.3) 28.5–47.3
Tg-Abs titer [IU/mL] mean (SEM) range	319.2 (295.7) 214–546	329.3 (254) 212–634	102.9 (71.4) 49.5–183.0	114.6 (93.5) 39.3–161.7	91.3 (76.6) 29.5–137	89.3 (88.3) 53.4–192.6
Thyroid volume [mL/m ²] mean (SEM) {Me; min–max}	21.0 (3.4) {19.0; 17.8–25.4}	24.9 (5.7) {21.8; 20.8–25.4}	19.0 (2.4) {17.2; 15.8–21.4}	21.6 (3.6) {18.8; 17.7–25.2}	17.5 (2.7) {16.9; 15.1–22.3}	20.9 (4.8) {17.6; 16.5–24.3}
Activity of ¹³¹ I [MBq] ([mCi])	800 (0.0) 22 (0.0)	800 (0.0) 22 (0.0)	800 (0.0) 22 (0.0)	800 (0.0) 22 (0.0)	555 (15) 555 (15)	555 (15) 555 (15)

TSH – thyroid stimulating hormone; fT4 – free tetraiodothyroxine; fT3 – free triiodothyronine; TPO-Abs – thyroperoxidase autoantibodies; Tg-Abs – thyroglobulin autoantibodies; TSHR-Abs – autoantibodies to the thyrotropin receptor; ¹³¹I – radioiodine; mCi – millicurie; SEM – standard error of the mean; min – minimum; max – maximum; Me – median. Data are given as n, mean (SEM, range, %). Normal values in our laboratory are as follows: fT4: 11.5–21.5 pmol/L; fT3: 3.9–6.8 pmol/L; TSH: 0.27–4.2 μ U/mL; TSHR-Abs: <2 IU/L, TPO-Abs: 0–34 IU/mL and Tg-Abs: 10–115 IU/mL. All patients had undetectable serum Tg-Ab, TPO-Ab and TSHR-Abs. Thyroid volume was measured with ultrasonography (normal values range up to 19 mL for F and up to 25 mL for M).

Results

Of the 678 patients assessed, 109 were eligible for inclusion in this study. The reasons for ineligibility were: incomplete medical records for 38 (35%) patients (27 women and 11 men), retrosternal goiter in 35 (32%) patients (23 males and 12 females); severe Graves’ ophthalmopathy in 13 (12%) female patients, and mental disease in 11 (10%) patients, while 12 (11%) patients did not agree to participate.

The demographic, clinical and laboratory characteristics of the cohort at presentation are summarized in Table 1A,1B. Between 2005 and 2016, we were able to obtain follow-up data for 569 hyperthyroid patients with reduced RAIU at baseline (<30%). Of these, 284 were classified as suffering from GD (228 women and 56 men), 231 (153 women and 78 men) developed TMG and 54 (31 women and 23 men) were assigned to the group with TA.

Adjuvant lithium increased RAIU in all hyperthyroid patients (Table 2). For the hyperthyroidism Li(–) and Li(+) groups, respectively, the RAIU at the following time points (T) was: T_{5h}, 11.9 ±5.6% compared to 23.9 ±10.1% (p < 0.001); T_{24h}, 25.9 ±8.3% compared to 40.5 ±12.4% (p < 0.05); T_{48h}, 27.8 ±8.1% compared to 40.9 ±13.7% (p < 0.05); T_{72h}, 26.2 ±10.2% compared to 39.5 ±11.2% (p < 0.01); and T_{96h}, 24.7 ±7.1% compared to 37.4 ±10.1% (p < 0.01). In the comparison group, RAIU was 31.3% ±10.2% at T_{5h}, 52.3% ±6.9% at T_{24h}, 54.9 ±12.7% at T_{48h}, 47.5 ±10.8% at T_{72h}, and 38.5 ±9.2% at T_{96h}.

In the Li(+) group, the RAIU before administration of lithium was 12.0 ±4.4% at T_{5h}, 25.0 ±5.4% at T_{24h} and 24.0 ±6.0% at T_{96h} (p > 0.05 for all 3 time points in comparison to the Li(–) group).

Table 1B. Clinical and biochemical characteristic of the Li(–) and Li(+) and comparison groups at baseline

Characteristic	Examined groups		Comparison group
	Li(–)	Li(+)	
Females (n, %)	222 (39.0)	190 (33.4)	57 (37.0)
Males (n, %)	83 (14.9)	74 (13.00)	21 (27.0)
Age of females, mean (range) [years]	52 (32–81)	53 (29–87)	51 (19–59)
Age of males, mean (range) [years]	51 (26–83)	55 (27–86)	47 (21–52)
Week of diagnosis	13–27	11–20	12–25
Mild ophthalmopathy			
yes (%)	96 (17)	102 (18)	46 (59)
no (%)	209 (37)	162 (28)	32 (41)
TSH level [mIU/L]			
mean (SEM)	0.09 (0.07)	0.0 (0.12)	0.0 (0.04)
range	0.0–0.23	0.01–0.22	0.00–0.19
Free T3 level [pmol/L]			
mean (SEM)	5.6 (3.6)	8.2 (4.1)	5.6 (3.3)
range	3.3–12.7	3.9–6.2	3.1–7.4
Free T4 level [pmol/L]			
mean (SEM)	26.0 (4.5)	29.3 (5.8)	27.4 (6.7)
range	25–32.5	20.4–32.3	21.9–33.6
TSHR-Abs titers [IU/L]			
mean (SEM)	4.7 (2.2)	3.6 (1.9)	6.7 (2.8)
range	0.9–13.4	1.1–5.7	2.4–11.2
TPO-Abs titers [IU/mL]			
mean (SEM)	149.7 (135.3)	117.0 (114.2)	189 (345.8)
range	39.1–190.5	64.5–195.0	116.0–1285.0
Tg-Abs titer [IU/mL]			
mean (SEM)	171.1 (147.9)	177.3 (145.3)	231.7 (198.4)
range	97.6–307.2	113.2–329.4	98.2–1121.0
Thyroid volume [mL/m ²]			
mean (SEM)	15.6 (2.9)	18.9 (3.6)	21.5 (4.7)
{Me; min–max}	{15.7; 14.1–54.1}	{16.5; 13.4–43.3}	{17.5; 16.4–42.3}
Activity of ¹³¹ I [MBq] ([mCi])	814 (22)	814 (22)	185.0–814.0 (5–22)

TSH – thyroid stimulating hormone; FT4 – free tetraiodothyroxine; FT3 – free triiodothyronine; TPO-Abs – thyroperoxidase autoantibodies; Tg-Abs – thyroglobulin autoantibodies; TSHR-Abs – autoantibodies to the thyrotropin receptor; ¹³¹I – radioiodine; mCi – millicurie; SEM – standard error of the mean; min – minimum; max – maximum; Me – median.

Data are given as n, mean (SEM, range, %). Normal values in our laboratory are as follows: FT4: 11.5–21.5 pmol/L; FT3: 3.9–6.8 pmol/L; TSH: 0.27–4.2 µU/mL; TSHR-Abs: <2 IU/L, TPO-Abs: 0–34 IU/mL and Tg-Abs: 10–115 IU/mL. All patients had undetectable serum Tg-Ab, TPO-Ab and TSHR-Abs. Thyroid volume was measured with ultrasonography (normal values range up to 19 mL for F and up to 25 mL for M).

Table 2. The mean iodine uptake values (RAIU) in all studied groups

Time of observation of RAIU [h]	5	24	48	72	96
Li (-) group [%]	11.9 ±5.6	25.9 ±8.3	27.8 ±8.1	26.2 ±10.2	24.7 ±7.1
Li (+) group [%]	23.9 ±10.1	40.5 ±12.4	40.9 ±13.7	39.5 ±11.2	37.4 ±10.1
Comparison group [%]	31.3 ±10.2	52.3 ±6.9	54.9 ±12.7	47.5 ±10.8	38.5 ±9.2

Thyroid hormone concentrations

For the Li(-) and Li(+) groups, differences in the serum level of fT3 (Fig. 1) were recorded at most time points ($p = 0.001$), except at 48 h and after 6 and to 12 months of follow-up. The initial concentration of fT3 in Li(+) patients was 8.2 ± 4.1 pmol/L, while that in ^{131}I Li(-) patients was significantly lower at 5.6 ± 3.6 pmol/L ($p < 0.001$). The fT3 level in ^{131}I Li(-) and ^{131}I Li(+) patients at each time point was as follows: after 24 h, 8.1 ± 3.9 pmol/L compared to 6.2 ± 3.2 pmol/L; after 48 h, 8.1 ± 3.9 pmol/L compared to 7.8 ± 4.1 pmol/L; after 72 h, 8.3 ± 4.4 pmol/L compared to 6.3 ± 3.9 pmol/L; after 96 h, 8.4 ± 3.4 pmol/L compared to 6.0 ± 3.1 pmol/L; after 1 month, 8.7 ± 4.5 pmol/L compared to 7.1 ± 5.1 pmol/L; after 6 months, 4.9 ± 3.1 compared to 5.1 ± 3.9 pmol/L; and after 1 year, 3.1 ± 3.7 pmol/L compared to 3.8 ± 3.9 pmol/L.

The baseline serum fT4 concentration in Li(+) patients was 29.3 ± 5.8 pmol/L, which was significantly higher than in Li(-) patients (26.0 ± 4.5 pmol/L; $p = 0.001$). However, after 24 h and up to 1 month into the observation period, the fT4 concentration was significantly lower in the ^{131}I Li(+) group compared to the ^{131}I Li(-) group ($p < 0.001$). After 24 h, it was 27.9 ± 3.9 pmol/L compared to 34.2 ± 7.4 pmol/L; after 48 h, it was 27.3 ± 3.8 pmol/L compared to 38.2 ± 5.2 pmol/L; after 72 h, it was 25.7 ± 4.8 pmol/L compared to 38.2 pmol/L ± 5.2 ; after 96 h, it was 24.8 ± 5.0 pmol/L compared to 38.2 ± 5.2 pmol/L; after 1 month, it was 29.3 ± 4.2 pmol/L compared to 39.7 ± 6.7 pmol/L; after 6 months, it was 21.2 ± 7.5 pmol/L compared to 19.5 ± 6.1 pmol/L; and after 1 year, it was 19.6 ± 6.4 pmol/L compared to 18.1 ± 3.9 pmol/L (Fig. 2).

Therefore, a significant reduction of fT4 and fT3 was observed in the Li(+) group compared to the Li(-) and comparison groups. This significant reduction was observed at each subsequent time point following ^{131}I .

Comparison of the mean TSH serum concentrations of patients before and after administration of Li did not show a statistically significant difference ($p > 0.05$). The average TSH level before administration of Li was 0.3 mIU/L, and after administration of Li it was 0.45 mIU/L. All patients who received Li underwent analysis of serum concentrations on the 7th day of application, obtaining values from 0.34 mmol/L to 0.49 mmol/L, with a mean value of 0.5 ± 0.06 mmol/L.

Clinical thyroid status

At 1 year, 462 patients (81.2%) were successfully treated (hypothyroid or euthyroid) and 107 (18.8%) remained hyperthyroid. Euthyroid status was achieved by about 10% of patients, including approx. 70% of Li(+) group patients with GD. In the group with TNG, this percentage was 43%, including 74.7% in the Li(+) group; in the TA group, this percentage was approx. 76%, including 71% in the Li(+) group. In addition, clinical signs were less pronounced during follow-up in patients in the Li(+) group. Among Li(+) group patients with GD, recurrent hyperthyroidism was observed in approx. 31% of patients with GD and 29% of patients with TMG, whereas no cases of recurrent hyperthyroidism were diagnosed in patients with TA, as judged from biochemical analysis, clinical symptoms and reduced demand for antithyroid medications (Table 3).

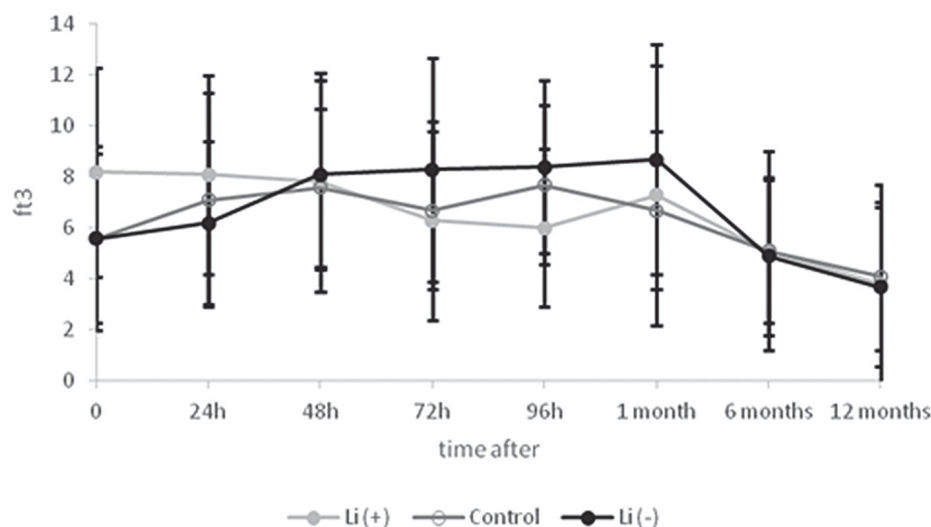


Fig. 1. Serum fT3 concentrations for the Li(-) and Li(+) groups and the comparison group at baseline and at each subsequent time point following ^{131}I administration

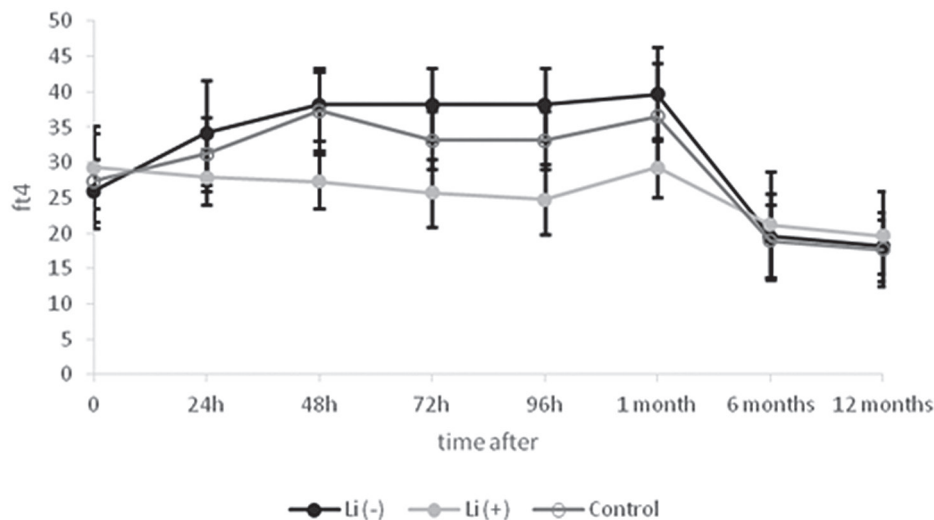


Fig. 2. Serum fT4 concentrations for the Li(-) and Li(+) groups and the comparison group at baseline and at each subsequent time point following ¹³¹I administration

Table 3. Clinical outcome of a single fixed dose (555(15mCi)* MBq or 740 MBq (20mCi) of radioiodine for all patients

[Empty cell]	Euthyroid (n, %) (Li(-), %/ Li(+), %)	Hypothyroidism (n, %) (Li(-), %/ Li(+), %)	Hyperthyroidism (n, %) (Li(-), %/ Li(+), %)	Treated with 1 st dose of ¹³¹ I (n, %) (Li(-), %/ Li(+), %)	Treated with 2 nd dose of ¹³¹ I (n, %) (Li(-), %/ Li(+), %)
GD (n = 284)	28 (9.8) 9 (32.1)/ 19 (67.9)	195 (68.6) 84 (43.1)/ 111 (56.9)	61 (21.6) 42 (68.8)/ 19 (31.2)	238 (83.8) 187 (78.6)/ 51 (21.4)	46 (16.2) 28 (60.9)/ 18 (39.1)
TMG (n = 231)	99 (42.8) 25 (25.3)/ 74 (74.7)	90 (39.0) 27 (30.0)/ 63 (70.0)	42 (18.2) 30 (71.4)/ 12 (28.6)	193 (33.9) 151 (78.2)/ 42 (21.8)	38 (6.7) 31 (81.6)/ 7 (18.4)
TA* (n = 54)	41 (75.9) 12 (29.3)/ 29 (70.7)	9 (16.7) 2 (22.2)/ 7 (77.8)	4 (7.4) 4 (100)/ –(–)	49 (8.6)* 29 (59.2)/ 20 (40.8)	5 (87.8) 3 (60)/ 2 (40)
All (mean) (n = 569)	168 (29.5) 46 (27.4)/ 122 (72.6)	294 (51.7) 113 (38.4)/ 181 (61.6)	107 (18.8) 76 (71.0)/ 31 (29.0)	480 (84.3) 367 (76.5)/ 113 (23.5)	89 (15.6) 62 (69.7)/ 27 (30.3)
Comparison group (n = 78)	21 (26.9)	40 (51.3)	17 (21.8)	63 (80.8)	15 (19.2)

* Administered activity of ¹³¹I in patients with toxic adenoma was in each case equal to 555 MBq (15mCi), while in other cases an “ablative” dose of 740 MBq (20mCi) of ¹³¹I was used.

Discussion

Li is as a normothyroidic drug widely used in psychiatry, thyrology and therapy for hyperthyroidism. Its mechanism of action is not fully understood, although it is believed to work similarly to iodine. Moreover, ionized lithium inhibits proteolysis of thyroglobulin,¹² inhibits T4 to T3 conversion,^{1,9} and reduces the concentration of thyroid hormone transport proteins in the blood serum.^{1,32} The data on the effect of Li on thyroid iodine in the literature is divergent. An increase in iodine uptake after administration of Li was described by Sedvall et al.³² The authors demonstrated that Li administered for 12 consecutive days resulted in a decrease in the level of protein-bound iodine in all 7 patients, alongside an increase in iodine uptake from 26% to 36.7% after 24 h. Similar results were obtained in animals by Berens et al.³³ These authors also found that the increased ability of the thyroid to accumulate iodine

during Li administration is independent of the degree of prolonged iodine retention in the thyroid. In our study, administration of Li according to the proposed regimen caused a significant increase of RAIU in all patients after adjuvant therapy, and iodine uptake increased from approx. 12% to 24% and from 25% to 41% after 24 h in comparison to RAIU after 5 h. The results of our research, which are consistent with most of the data available in the literature, have demonstrated the significant role of lithium adjuvant therapy in increasing RAIU.

Different results were presented by Temple et al.³⁴ and Turner et al.³⁵ Temple et al. studied, among other things, the effect of Li on thyroid RAIU in 11 patients with hyperthyroidism. The initial iodine uptake of T_{24h} in this group was 33 ±88% and did not change during administration of 900 ±1500 mg of Li for 10 days. Turner et al.,³⁵ on the other hand, administered 400 mg of Li for 1 week before and continued for 1 week after administration

of a standard therapeutic dose of radioiodine (5 mCi). The T_{24h} at baseline in this group was approx. 70%, while after administration of Li it was 67%. Summarizing the obtained results, the authors emphasized the fact that Li only affected the effective half-life of iodine, but did not affect iodine uptake. The basic difference between the groups studied by Sedvall et al.,³² Turner et al.³⁵ and Temple et al.³⁴ concerns the initial iodine uptake. In a study by Sedvall et al.,³² it amounted to 26%, as mentioned above, while in a study by Turner et al.,³⁵ it was 70%.

In the paper by Bogazzi et al. additional studies were carried out on a group of patients for whom the iodine uptake T_{24h} was at least 30%.¹³ The administration of Li to this group did not significantly increase iodine uptake. Given the literature data and our own observations, it should be assumed that the Li effect depends on the initial value of T_{24h} . If the initial iodine uptake is relatively high, Li may not affect this parameter; however, if it is lower, it should be assumed that Li will likely cause it to increase. As noted above, this is certainly not the only parameter determining the effect of Li. In some patients with reduced T_{24h} , the administration of Li may not have the desired effect. The basic condition for conducting radioisotope treatment of patients with hyperthyroidism is adequately high retention of radioiodine in the thyroid gland. In some patients, it is so low that the use of radioactive iodine is impossible or involves a much higher dose of radioactivity, especially after treatment with amiodarone²⁶ or shading agents.³⁶

The results of our study confirm the present observations²⁹ and indicate that even a few days of administration of Li results in favorable changes in thyroid hormone levels in blood serum, such as decreases in the fT3 and fT4 levels, and has no effect on the TSH level. This result certainly depends on the inhibitory effect of Li on thyroglobulin proteolysis and the secretion of thyroid hormones into the bloodstream. In our study, the serum level of fT3 at baseline in the Li(+) group was 8.2 ± 4.1 pmol/L and after T_{96h} it was 6.0 ± 3.1 pmol/L; fT4 at baseline was 29.3 ± 5.8 pmol/L and after T_{96h} it was 24.8 ± 5.0 pmol/L. The significant effect of short-term administration of Li on the T3 level can result from a decrease in the concentration of transport proteins (TBG), which was previously described, but mainly results from inhibition of the conversion of T4 to T3. Jarlov et al.²⁴ concluded that administration of Li at a dose of 32.4 mEq/day led to a decrease in the level of T4 by 13% on the 3rd day of the regimen and a 27% decrease by the 10th day, whereas the decrease in the concentration of T3 in the blood serum (resin test) was 16% and 38% on the 3rd and 10th day, respectively.

Data concerning changes in the concentration of thyroid hormones 1 week after administration of a radioisotope can be found in a publication by Bogazzi et al.¹³ and our earlier research.²¹ Bogazzi et al.¹³ evaluated the effect of the administration of Li on the course of treatment with ¹³¹I in patients with GD. The authors observed a transient

increase in fT3 and fT4 and an increase in the thyroglobulin level in patients who did not take Li. These changes are likely caused by the direct destructive action of ionizing radiation on follicular cells. This phenomenon was not observed in patients additionally treated with Li. Similar observations were reported by Martin et al.²⁷ In our results, which do not deviate significantly from that study, the levels of thyroid hormones after administration of ¹³¹I were evaluated after 1, 6 and 12 months. It was shown that in this period, the group of patients receiving Li was characterized by significantly lower levels of thyroid hormones. This phenomenon is extremely beneficial in the initial period of radioiodine treatment as it allows for faster euthyrosis than in patients who do not receive Li. Furthermore, it likely allows for avoiding transient increases in thyroid hormone levels as a result of ionizing radiation in the initial period after the administration of ¹³¹I.

Our findings indicate that the administration of Li for a short period of time does not cause significant changes in serum TSH levels. The TSH was normalized only a few months after the administration of ¹³¹I. Similar results have been reported by other authors.^{31,33,37}

This paper presents a different method of determining the therapeutic activity of radioiodine than used in previous publications on the therapeutic effects of ¹³¹I and Li. The recommended dose determination method has now been adopted in clinical practice. The administered ¹³¹I activity of ¹³¹I in patients with toxic adenoma was in each case equal to 555 MBq (15 mCi), while in other cases, an "ablative" dose of 740 MBq (20 mCi) of ¹³¹I was used. Despite the use of such a high ¹³¹I activity for ¹³¹I, 22% of patients should have been treated with the second activity of ¹³¹I. Previous studies used the standard dose³⁸ or calculated the radioactivity used per 1 g of tissue.³¹ Despite these methodological differences, the curative effects shown in the cited works and in our study are similar. The administration of Li had a positive effect on the efficacy of radioisotope treatment in the early period after the administration of ¹³¹I.

At one-year follow-up, in the group of patients with GD with Li(+), hyperthyroidism persisted in approx. 31% of patients after administration of Li, while remission euthyroidism and hypothyroidism were obtained in 67% and 57% of patients, respectively (Table 3). In the Li(+) group with TMG, recurrent hyperthyroidism was observed in 28.6% of patients, whereas in patients with TA, no cases of recurrent hyperthyroidism were diagnosed, as judged from biochemical analysis, clinical symptoms and reduced demand for ATD. In the group with toxic nodular goiter, the percentage of successfully treated patients in the Li(+) group was approx. 25% (euthyroidism) and 70% had hypothyroidism; in the toxic adenoma group, it was approx. 70% (euthyroidism) and in the Li(+) group of patients, it was approx. 78% (hypothyroidism). Additionally, clinical signs were less pronounced during follow-up in patients with

Li(+). Similar percentages were observed for the control group, with hyperthyroidism found in 21.8% of patients and remission in 78.2% of patients. Our observations were confirmed by Bogazzi et al.,³¹ who demonstrated that adjuvant lithium therapy is more effective, as evidenced by the fact that much better theranostic effects were obtained. Most patients (approx. 84%, with Li(+)) were given a single therapeutic dose of radioiodine.

No significant side effects (e.g., nausea, diarrhea and anorexia) were reported in the studied group of patients after administration of Li. Bogazzi et al.³¹ used a similar treatment protocol (298 patients treated with combined ¹³¹I and Li therapy) and reported nausea in 19.4% of patients and polyuria in 23.9% of patients, although these changes were not statistically significant.

Burrow et al.³⁹ observed side effects in only 2 of 13 patients receiving 900 mg of Li per day. The side effects consisted mainly of enlargement of the thyroid gland. However, goiter regressed after cessation of treatment. In 2015, the European Medicine Agency announced that long-term use of lithium might induce renal tumors. However, a recent study by Ambrosiani et al.⁴⁰ based on 33 years of observation of 1871 lithium patients (clinical records) clearly demonstrated low rates of and mortality due to thyroid or renal cancers in patients receiving permanent adjuvant lithium therapy.

In our study, due to the therapeutic activity of ¹³¹I, no thyroid goiter was observed in any case. In all cases, goiter was significantly reduced, which was the aim of this treatment.

Limitations

Our study has some limitations. Firstly, we could not study the level of urinary iodine excretion in this group of patients as an indicator of the overall iodine pool in the body. Therefore, it is assumed that a significant reduction in thyroid iodine uptake capacity as a result of the increased overall pool of iodides in the body might be a possible determinant of Li inefficiency. Secondly, our study did not analyze the titer of the thyroid antibodies in serum; however, it has not been previously observed that short-term administration of Li results in intensification of clinical symptoms (e.g., infiltrative exophthalmos).

Conclusions

The results of this study of a large cohort of patients with different types of hyperthyroidism (GD, TMN and TA) suggest that a short course of adjuvant lithium and ¹³¹I therapy is feasible, highly effective and safe, particularly in patients with low RAIU. Lithium therapy may be a valuable adjunct in this group of patients to reduce thyroid hormone levels.

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