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Lithium carbonate pre-treatment in 131-I therapy of hyperthyroidism

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Abstract

BACKGROUND: The aim of the present work was to investigate the influence of lithium carbonate on the kinetics of radioiodine in the thyroid gland, and the long-lasting effect of radioiodine therapy pre-treated with lithium carbonate in patients with different types of hyperthyreosis and low baseline 24-h thyroidal radioactive iodine uptake (RAIU).

MATERIAL AND METHODS: The examinations were performed in two groups of patients: in a control group with RAIU > 30% and in patients with RAIU < 30%. All groups were comparable with regard to age, sex, duration and type of disease (Graves' disease, autonomous node, multinodular goitre). The control group was treated (without lithium) according to described protocol. The second group was pre-treated with lithium carbonate in a dose of 1.0 g/day for 6 days before radioiodine and 3 days thereafter.

RESULTS: A significant increase in iodide uptake in the thyroid gland was observed during intake of lithium carbonate in 106 out of 128 patients. A decrease of T_3, FT_3, T_4, and FT_4 levels and no significant changes in concentration of TSH were observed as an effect of lithium carbonate treatment. Three years of follow-up show that the results of radioiodine therapy with short lasting lithium carbonate intake are better in the first year and are similar in the second and third years in comparison to the control group.

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CONCLUSIONS: Lithium pre-treatment in hyperthyroid patients with low baseline uptake of radioiodine can increase iodine retention in the thyroid gland independently of the primary disease and permits the use of lower doses of radiation in the therapy.
Key words: lithium carbonate, 131-Iodine, hyperthyroidism, Graves' disease, multinodular goitre, autonomous tumour

Introduction

Radioiodine has been used in the treatment of thyrotoxicosis for almost 60 years [1] and is still used as the method of choice in several types of thyroid diseases [2].

The dose of radioactivity given to a patient is calculated according to a dosimetric formula [2]. Patients with low RAIU should be treated with significantly higher activities to obtain similar therapeutic effects, or other therapeutic options should be considered.

Lithium salts significantly change the iodine kinetic in thyroid tissue through the inhibition of the release of organic iodine from the thyroid gland [3–6]. This effect suggests that lithium may be useful as an adjunct to radioiodine therapy in thyrotoxicosis.

The aim of this work was to evaluate whether lithium carbonate pre-treatment will change the iodine uptake in hyperthyroid patients with initially low RAIU. We assumed that lithium carbonate pre-treatment increases iodine retention; therefore, patients with low baseline RAIU can be treated successfully with lowered risk of radiation. Our results, as we will show, suggest that lithium carbonate pre-treatment in patients with RAIU < 30% is an effective and profitable method of treatment, independent of the type of disease.

Material and methods

A total of 256 patients with newly diagnosed hyperthyreosis were enrolled over four years. All patients were older than 20 years of age, and the diagnosis of hyperthyroidism was made in the preceding 6 months. Patients with previous treatment of hyperthyroidism with radioiodine or surgery or with contraindications to lithium treatment were excluded.

Patients were treated with methimazole for 2–3 months to restore euthyroidism. Methimazole was withdrawn 15 days before

examinations and then radioiodine uptake in the thyroid gland was measured. Hyperthyroid patients (Graves' disease, multinodular goitre and autonomous tumour) were divided into two groups according to the baseline 24-hour RAIU: higher or lower than 30%. Both groups were matched according to the type and duration of the disease, age, and sex as possible factors influencing the results. All patients gave informed consent.

In order to evaluate if the effect of lithium carbonate on radioiodine kinetic is dependent of baseline iodine uptake, we examined additionally ten hyperthyroid patients with RAIU > 30% before and during lithium treatment.

A total of 128 patients had low RAIU (Group I). In this group kinetic examinations of iodine uptake were repeated after lithium carbonate was included at a dose of 1.0 g per day (2 × 0.5 g). Lithium carbonate was added 3 days before the start of iodine kinetic examinations and was continued until the fifth day. When lithium carbonate pre-treatment caused an increase in RAIU a therapeutic dose of radioiodine was calculated and implemented. Lithium carbonate was given for an additional five days after application of the therapeutic dose of [131]I.

In 45% of patients (n = 51) in this group we were able to make a three-year systematic observation after ^{131}I treatment.

The other 128 patients with RAIU > 30% (Group II) followed the same protocol but without lithium carbonate pre-treatment.

Iodide uptake was measured over five days. At the end of the kinetic studies the therapeutic dose of ^{131}I was calculated and given. From this cohort 51 patients (as a randomised control group) were also systematically observed over a 3-year period.

The therapeutic dose of radioiodine was calculated according to a dosimetric formula [2].

The radiation dose in each type of disease was similar in both groups: in Graves' disease — 80 Gy, in multinodular goitre — 200 Gy, and in autonomous tumour — 400 Gy. The mean dose

of radioiodine in the omised control group was 580 MBq (290–830 MBq) and in the lithium treatment group 650 MBq (325–900 MBq).

Table 1 shows the number of patients and type of disease when the kinetic of radioiodine was measured, and Table 2 presents the number of patients, radioiodine therapeutic dose, and the type of disease in whom the effect of therapy was analysed.

Baseline evaluations included: clinical examination, thyroid scan, thyroid uptake of radioiodine after 6, 24, 48, 72, 96, and 120 hours, thyroid ultrasonography, white cell count, differential count, haematocrit, mean corpuscular volume, platelet count, creatine, serum electrolytes, urinary analysis, and electrocardiogram. Serum total and free T4 (FT4), T3 (FT3), and TSH levels were measured. The normal ranges were: serum T4, 55–160 nmol/l; FT4, 8.4–23.2 pmol/l; T3, 1.3–3.0 nmol/l; FT3, 3.8–8.4 pmol/l; and TSH, 0.4–3.7 mU/l. The measurements were performed at the beginning of lithium carbonate application, immediately before iodine treatment (fifth day of lithium carbonate treatment), 7 and 14 days post radioiodine application, and then every 1-3 months for the whole of the follow-up period.

The concentrations of lithium carbonate in the serum were evaluated on the fifth day of treatment, and it was between 0.6 and 0.9 (0.8 ± 0.062) mEq/l. Thyroid volume was determined by ultrasound using a 7.5 MHz linear transducer and calculated by the ellipse model.

The clinical state of the patients was defined during each control visit and summarized every year after the treatment.

Statistical analysis

Baseline values were expressed as mean ± SD for quantitative variables. The baseline characteristics of the two groups were compared by unpaired t-test and by one-way analysis of variance. Bartlett test equality in variance was performed. All data were evaluated using the Stat-Graphics program.

Table 1. Baseline characteristics of patient study groups with hyperthyroidism in which iodine kinetic was evaluated

| | Type of disease Graves' disease multinodular goitre autonomous tumour | | | | | |
	Control	Lithium	Control	Lithium	Control	Lithium
No of patients	18	18	53	53	46	46
Mean age	62.2	59,9	51.4	53.2	56.3	58.2
Sex m/f	2/16	2/16	9/44	9/44	12/34	12/34

Table 2. Baseline characteristics of the patient study groups observed over 3 years after radioiodine treatment

| | Type of disease Graves' disease multinodular goitre autonomous tumour | | | | | |
	Control	Lithium	Control	Lithium	Control	Lithium
No. of patients	18	18	18	18	19	19
Mean age	58.4	57.1	50.2	51.4	53.2	55.1
Sex m/f	2/16	2/16	5/13	5/13	7/12	7/12
Radiation dose (Gy)	80	80	200	200	400	400
Therapeutic Activity (MBq)	260–470	260–540	480–925	480–925	630–800	600–925
Mean ± SD	120	145	150	165	205	215

SD — standard deviation

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Table 3. RAIU of radioiodine in the studied group

| | Type of disease Graves' disease multinodular goitre autonomous tumour | | | | | |
	Control	Lithium	Control	Lithium	Control	Lithium
T6	4% ± 3.2	28% ± 6.3	11% ± 2.1	34% ± 7.1	12% ± 2.4	30% ± 5.2
T24	26% ± 4.1	50% ± 5.2	24% ± 3.3	54% ± 6.6	25% ± 4.8	57% ± 6.4
T48	26% ± 3.8	48% ± 6.1	26% ± 4.1	50% ± 5.9	26% ± 4.2	54% ± 5.9
T72	24% ± 2.8	45% ± 5.1	24% ± 3.7	45% ± 4.8	25% ± 4.2	50% ± 5.6
T96	24% ± 2.4	40% ± 4.7	24% ± 3.5	43% ± 4.6	24% ± 4.2	47% ± 5.5

Results

There were no significant differences in the baseline clinical and biochemical characteristics between both study groups.

Radioiodine uptake before lithium intake

Table 3 presents the values of radioiodine uptake at different times of examination, respectively, in the group of patients with low RAIU and in the control group. The uptake of iodine in Group I at 6 and 24 hours was on average two-times lower compared with the control group. There were no statistically significant differences between the studied groups in effective and biological half life time for radioiodine. Calculated effective half-life times were: 6.5 ± 0.9 and 6.3 ± 0.7 days, respectively, and biological half-life times were 26 ± 1.9 days and 23 ± 1.5 days, respectively.

Kinetic of iodine during lithium carbonate application

In all ten patients with RAIU > 30% in whom the effect of lithium carbonate was separately studied, no effect of lithium carbonate pre-treatment on radioiodine uptake was noted. The baseline uptakes after 6 and 24 hours were 31 ± 6% and 43 ± 4.6%, respectively, and during lithium treatment 32 ± 8% and 41 ± 6.7%, respectively. Despite this increases in biological and effective half-life times were observed: biological half-life time increased from 22 ± 12 days to 211 ± 15 days, and effective half-life time from 5.9 ± 2 days to 7.1 ± 1.6 days. There were three patients with Graves' disease, three patients with multinodular goitre, and four patients with autonomous tumour.

When lithium carbonate was given to the patients with low RAIU, two types of response were noted.

First, in 22 patients we did not observe any effect of lithium carbonate treatment (1 with Graves' disease, 11 with multinodular

goitre, and 10 with autonomous adenoma). The baseline uptakes of iodine after 6 and 24 hours were 7 ± 3% and 19 ± 6%, respectively, and during lithium carbonate intakes were 8 ± 4% and 19 ± 7%, respectively. Despite this lack of response on RAIU, a significant prolongation of the biological and effective half-life times were observed. The biological half-life time increased to 240 ± 14 days and effective half-life time to 7.8 ± 0.5 days (p < 0.005). On the basis of clinical history, incidences of iodine overloading were documented 8–20 months before examinations in all cases.

Second, a significant increase in iodine retention was noted in 106 patients (p< 0.001). The biological half-life time increased to 267 ± 24 days (p < 0.001) and effective half-life time to 7.8 ± 0.8 days (p < 0.001). An analysis of iodine uptake in response to the lithium carbonate treatment and correlation with type of disease was performed (Table 4).

The increase in RAIU was significantly higher in the group of patients with Graves' disease and autonomous adenoma in comparison to the patients with multinodular goitre (p < 0.05).

The effect of lithium treatment on the level of thyroid hormones

Our results (in the group of 128 patients) show that lithium carbonate influenced the T_3 and T_4 plasma levels (p < 0.001) as well as FT_3 and FT_4 levels (p < 0.005) in the initial five-day period of treatment.

No effect of lithium carbonate on the level of TSH in the presented group was seen (Table 5).

The level of T_4 decreased significantly on the fifth day of lithium carbonate treatment, on average, by 10% and T_3 by 40%. FT_4 decreased, on average, by 33% and FT_3 by 9%. The beneficial effect of lithium carbonate on the thyroid hormones was also observed

Table 4. Iodine uptake before and during lithium carbonate treatment in responded group of patients in different types of hyperthyreosis

| | Type of disease Graves' disease multinodular goitre autonomous tumour | | | | | |
Lithium intake	Before	During	Before	During	Before	During
No. of patients	22	22	45	45	39	39
T6	14 ± 2.9	23 ± 4.2	11 ± 2.1	19 ± 2.4	12 ± 3.1	22 ± 3.8
T24	26 ± 3.9	41 ± 5.1	24 ± 1.9	35 ± 2.3	25 ± 2.8	41 ± 3.4
T48	26 ± 3.7	38 ± 4.8	26 ± 2.0	36 ± 2.4	26 ± 3.1	4.2 ± 3.3
T78	24 ± 3.7	37 ± 4.5	24 ± 2.3	34 ± 2.1	25 ± 2.7	41 ± 2.9
T96	24 ± 3.9	35 ± 4.3	24 ± 2.4	33 ± 2.0	24 ± 2.5	39 ± 3.1

Table 5. The level of thyroid hormones during lithium carbonate and radioiodine treatment

Time	T4 [nmol/l]	FT4 [pmol/l]	T3 [nmol/l]	FT3 [pmol/l]	TSH [mU/l]
Before treatment	120 ± 12	25.2 ± 4.1	2.5 ± 0.4	7.5 ± 0.5	0.15 ± 0.03
5th day of Lithium	108 ± 9.2	19.5 ± 2.8	1.5 ± 0.3	6.7 ± 0.5	0.20 ± 0.02
7th day after 131I application	98 ± 9.3	16.7 ± 4.2	1.3 ± 0.2	6.5 ± 0.3	0.12 ± 0.03
14th day after 131I application	92 ± 10.2	14.0 ± 1.1	1.1 ± 0.3	6.5 ± 0.3	0.12 ± 0.03

Table 6. The level of thyroid hormones after radioiodine treatment in the control group

Time	T4 [nmol/l]	FT4 [pmol/l]	T3 [nmol/l]	FT3 [pmol/l]	TSH [mU/l]
Before treatment	126 ± 15	26.4 ± 3.8	2.3 ± 0.4	7.1 ± 0.4	0.11 ± 0.04
7th day after 131I application	124 ± 10	23.8 ± 0.3	2.3 ± 0.2	7.3 ± 0.3	0.12 ± 0.03
14th day after 131I application	125 ± 12	25.2 ± 0.4	2.1 ± 0.3	6.8 ± 0.3	0.12 ± 0.03

after radioiodine application. There was no change in thyroid hormone levels in the control group during this period (Table 6).

Long-term therapeutic effects of radioiodine treatment

A significantly better outcome was noted in the first group of patients one year after therapeutic radioiodine application.

The euthyreosis was observed in 84%, hypothyreosis in 4%, and hyperthyreosis in 12% of patients in the group treated by lithium carbonate. In the control group 50% of patients were euthyroid, 10% hypothyroid, and 40% hyperthyroid ($p < 0.05$). In the second and third years after treatment the results were comparable in both groups. There was no relation between efficiency of the lithium carbonate pre-treatment and the type of disease (Table 7).

Discussion

In the present study we evaluated the effect of lithium carbonate on 131I retention in the thyroid gland, on thyroid hormone levels, and the late effects of 131I treatment in hyperthyroid patients with decreased baseline RAIU in different types of hyperthyreosis. The effect of lithium carbonate pre-treatment was documented on the basis of three years of observations.

We recommend this method as a useful tool in this group of patients.

The results show several beneficial effects of lithium carbonate pre-treatment in most patients with low baseline RAIU:

— a significant increase in radioiodine retention;
— faster stabilization of the thyroid hormones;
— significantly better clinical outcome after the first year and similar therapeutic effect during the second and third years of observation after radioiodine treatment.

The beneficial effect of lithium carbonate as an adjunct to the radioiodine treatment in benign thyroid diseases has been reported previously by others [3–6], but the number of observed patients was relatively small or the period of clinical observation was relatively short. This effect was also observed in thyroid cancer [7–10].

The effect of lithium carbonate on RAIU

Our results show that lithium treatment could produce different effects on radioiodine accumulation in the thyroid gland: in patients with RAIU > 30% no effect of lithium carbonate on radioiodine uptake in the thyroid gland was noted. In patients with low baseline RAIU the effect of lithium carbonate was inhomogeneous: in most patients it produced a significant increase of iodine uptake but in 17% of cases no effect of lithium carbonate on RAIU was observed. All non-respondents to the lithium carbonate with low RAIU had a well-documented history of iodine overloading in the last 8–20 months before examination. It seems that this is a possible factor responsible for the lack effect of lithium salts on RAIU in some patients with decreased baseline uptake of radioiodine.

Different effects of lithium carbonate on iodine uptake are described in the literature [4, 11–14]. Taken together, the latest

Table 7. Effectiveness of 131I treatment in the control group and in the lithium carbonate pre-treated group

| | 1st year | | 2nd year | | 3rd year | |
	Control	Lithium	Control	Lithium	Control	Lithium
Euthyreosis	25 (50%)	42 (84%)	37 (74%)	42 (84%)	34 (68%)	37 (74%)
Hyperthyreosis	20 (40%)	6 (12%)	5 (10%)	2 (4%)	2 (4%)	0
Hypothyreosis	5 (10%)	2 (4%)	8 (16%)	6 (12%)	13 (28%)	13 (26%)

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and our results, it seems that the effect of lithium carbonate on radioiodine uptake was dependent on different characteristics of the examined groups: duration or dose of lithium treatment and especially on baseline level of RAIU.

Our results confirm previous observations that lithium carbonate is able to slow the release of iodide from the thyroid [5, 14, 15]. Biological and effective half-life times were increased significantly and independently of the effect of lithium carbonate on the iodine uptake. Similar results have been reported by others [11, 12].

This effect, as described previously, is probably caused by lithium action on tyreoglobulin [12, 16, 17]. It was concluded [5, 10] that this mechanism is responsible for the beneficial effect of lithium carbonate on the ^{131}I treatment.

The effect of lithium carbonate on thyroid hormone levels

Our results show that short-term lithium carbonate treatment influenced the dynamic of T_3 and T_4 concentrations in the serum as compared with the control group. Therefore, we suggest that lithium pre-treatment is a useful adjunct to radioiodine therapy to achieve more effective control of hyperthyroidism. The effect of lithium carbonate on thyroid hormones level was previously noted by others [6, 16]. Our results show that this effect is not only presented in patients with Graves' disease; it was also observed in patients with autonomous tumour and multinodular goitre.

No effect of short lithium carbonate treatment on the serum TSH level was observed in this study. Similar data have been described by others [6, 15]. Our results show that this effect is not dependent on the type of hyperthyreosis. The lack of increase in TSH is specially valuable in the use of lithium carbonate pre-treatment. It seems that lithium carbonate treatment does not provoke an increase in radioiodine uptake via TSH mechanism in the peritumoral tissue. It is not possible to exclude direct action of lithium ions on normal thyroid tissue, which can provoke an increase in iodine accumulation in normal follicular cells, but in our opinion this mechanism is not crucial from a clinical point of view in these groups of patients; the number of hypothyroid patients with autonomous tumour or multinodular goitre after lithium pre-treatment was lower in the first year after radioiodine treatment.

Lithium carbonate and the late effects of radioiodine treatment

The results confirmed a beneficial effect of lithium treatment on radioiodine therapy in the group of patients with low baseline accumulation of iodide, compared to the control group with normal iodide uptake. The effect was statistically significant in the first year after radioiodine application and similar to the control group in the second and third years of observation. Our results are in accordance with the data of Brownline et al. [18], who concluded that the addition of lithium to radioiodine did not produce a higher rate of cure after three years of follow-up.

In both examined groups of patients therapeutic doses of radioiodine were estimated according to a dosimetric formula, which is based on the absorbed radiation dose. It meant that both groups of patients were given similar radiation doses with respect to the disease. Until now, all observations concerning the beneficial effects of lithium on radioiodine treatment have been analysed in patients when the therapeutic activity of the radioiodine was based

on the fixed-dose method [14] or MBq per gram of thyroid tissue [6]. None of these methods was able to define the exact absorbed dose of radioactivity as a true dosimetric qualitative parameter of the effect of ionising rays.

The improved long-term results of radioiodine treatment in the group of patients in which lithium carbonate was given (despite similar absorbed dose) suggest that the mechanism of the lithium effect is dependent not only on prolongation of iodide decrease from the thyroid gland or increase in radioiodine retention; we suggest that other mechanisms can be responsible for the beneficial effect of lithium.

Our results show that the use of lithium carbonate enabled significantly lower doses of radioactivity to be used in patients with low baseline uptake of radioiodine in comparison with the calculated dose before lithium carbonate pre-treatment, not only in Graves' disease but also in other types of thyroid disease. The radioactivity given to a patient with diminished based RAIU can be reduced during lithium carbonate pre-treatment by about 80–100%. It is particularly beneficial in young patients in whom the total body-radiation dose must be kept to a minimum.

Toxicity

There are a few studies which have shown that long lasting treatment with lithium can provoke subclinical hypothyreosis, rare hyperthyreosis, or goitre [9, 20, 21]. Some side effects and toxicity of the lithium have been reported: nausea, diarrhoea, abdominal pain, polyuria, and leukocytosis. No complications directly produced by lithium were observed in the present study. We suggest that a relatively small dose of lithium (1.0 g/day) and short-lasting pre-treatment (eight days) is safe for patients and does not lead to the described complications.

In summary, lithium carbonate pre-treatment in patients with low uptake of radioiodine produced a significant increase in radioiodine retention in most patients and prolongation of the effective half-life time. The protocol presented in this report gives good results of radiotherapy of benign thyroid diseases in long-lasting periods and significantly decreases the therapeutic dose of radioiodine.

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