

Short term treatment with lithium carbonate as adjunct to radioiodine treatment for long-lasting Graves' hyperthyroidism

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Hell J Nucl Med 2015; 18(3): 186-188

Epub ahead of print: 18 November 2015

Published online: 5 December 2015

Abstract

Objective: Lithium carbonate is primarily used for the treatment of patients with bipolar affective disorders. Initial treatment of Graves' hyperthyroidism (GHT) with antithyroid drugs (ATD) has limitations at over 50% of treated patients because of significant side effects and relatively high relapses of the disease after drugs withdrawal. Till now, the influence of LiCO_3 on RIT outcome was mainly studied in patients with recent onset of GHT, and results were contradicted. Meta-analysis of case-control studies showed higher rated hypothyroidism in patients with mood disorders treated with LiCO_3 (121/869) than in controls (10/578). Although in a small number of patients ($n=28$) with long-lasting GHT, preliminary results of ours showed that ^{131}I treatment with LiCO_3 for 7 days significantly improved the efficacy of RIT versus the non- LiCO_3 treated patients ($P<0.001$). Lithium treated patients were cured faster (12 of 13 patients were cured after one month) than those treated only with ^{131}I (8 patients were cured after one and 11/15 patients after 12 months). Fewer patients treated with ^{131}I and LiCO_3 had persistent hyperthyroidism than those treated with ^{131}I alone. There were no toxic effects of LiCO_3 during 7 days treatment. **Conclusion:** These observations indicate of that short-term treatment with LiCO_3 in GHT patients as adjunct to ^{131}I -NaI improves the efficacy of RIT, prevents transient exacerbation of hyperthyroidism, early induction of hypothyroidism and does not worsen ophthalmopathy.

Introduction

Graves' hyperthyroidism (GHT) is the main type of Graves' disease (GD) characterized by the presence of biochemically confirmed antithyrotropin receptor autoantibodies (TRAb) and the clinical evidence of signs and symptoms of thyroid hyperfunction. Thyrotropin receptor autoantibodies are directed to thyroid stimulating hormone (TSH) receptors expressed on the thyroid epithelial cell surface and generate a diffuse proliferation of thyroid tissue and the hyperproduction and secretion of thyroid hormones [1, 2]. The possibility relapses and side effects of LiCO_3 have been extensively studied [3, 4].

Therefore, there is general agreement that if an 18 months ATD treatment fails or GHT relapses, the disease must be treated by radioiodine (^{131}I) treatment (RIT) or thyroidectomy [4, 5]. A crucial factor for the outcome of RIT in GHT is the ^{131}I uptake and the effective half-life (EHL) of ^{131}I in the gland [6, 7]. Thus, any attempt to prolong the EHL of ^{131}I may lead to improvement of RIT efficacy in patients with GHT. It was observed that the short-term treatment with LiCO_3 extends the ^{131}I half-life and increases the applied thyroid radiation dose without affecting the thyroid ^{131}I uptake [8-11].

Although toxic effects of LiCO_3 have been reported [12-14], the clinical use of LiCO_3 in hyperthyroidism has been extensively studied [15-17].

Lithium carbonate is primarily used for the treatment of patients with bipolar affective disorders [18]. Its long-term use has a potential to affect various aspects of thyroid function. Meta-analysis of case-control studies showed higher rated hypothyroidism in patients with mood disorders treated with LiCO_3 (121/869) than in controls (10/578) [19].

However, short-term treatment with this LiCO_3 has antithyroid properties similar to stable iodine and it has been used in the past to treat thyrotoxicosis [17, 20-22]. Dunkelmann et al. (2006) showed that LiCO_3 when given in a daily dose of 885mg for two weeks delayed the ^{131}I half-life by 60%, and increased the applied thyroid radiation dose by 39% without affecting thyroid ^{131}I uptake. These properties seem beneficial in relation to RIT. Nevertheless, the exact mechanism of action at the neuronal and thyroid cellular levels is at present still unclear. Lithium carbonate has been used clinically in order to potentiate the therapeutic effects of RIT [12-16, 23-25].

In addition, to its proven efficacy for prophylaxis and stabilization of mood in these patients [26-28], the use of LiCO_3 is acco-

panied by controversies related to life-long dosing and serum concentration monitoring as well with the tolerability of LiCO_3 consisting in possible appearance of both acute and chronic adverse effects [29]. Although the exact mechanism of action is still unclear [18], LiCO_3 has simple pharmacokinetics. One to six hours after oral administration, LiCO_3 is rapidly absorbed through the upper gastrointestinal tract and reaches peak serum concentrations during the next 4–12 hours. Due to the lower permeability of the blood-brain barrier, the corresponding peak concentration in the brain occurs 24 hours after LiCO_3 administration [30]. Lithium is exclusively excreted via the kidneys and any acute or chronic disturbance of its excretion, dramatically increases serum concentration and which may become toxic [29–31]. The pathophysiology of renal toxication, parathyroid and of thyroid dysfunction related to LiCO_3 administration is unclear [31].

Although in a small number of patients ($n=28$) with long-lasting GHT, our preliminary results showed that treatment of ^{131}I together with LiCO_3 for 7 days improved the efficacy of RIT ($P<0.001$). These still unpublished results, despite differences in the daily dose of LiCO_3 and in the time of starting treatment with ^{131}I [12–16, 23–25], are similar to those of other studies [12–14, 24, 25]. Lithium-treated patients were cured more rapidly than those treated only with ^{131}I . Furthermore, treated patients became hypothyroid earlier (at the 1st month) than patients treated only with ^{131}I (at the 3rd month). On the contrary, all cured patients treated with ^{131}I alone became rapidly hypothyroid up to the 9th month of treatment (Figure 1).

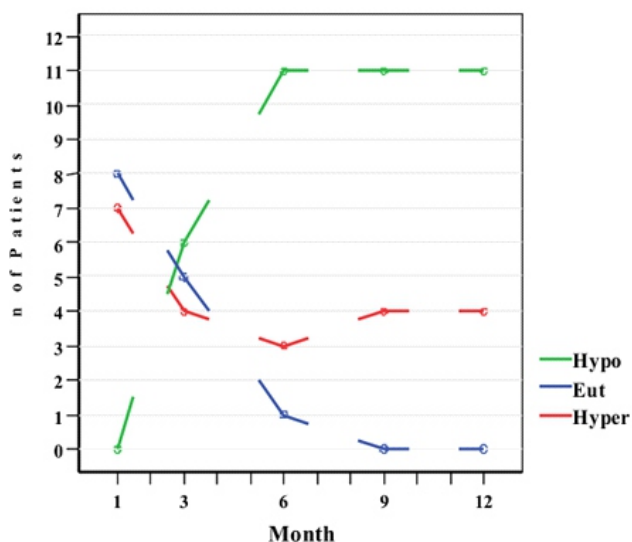


Figure 1. Radioiodine therapy response during 12 months follow-up period in patients with Graves' hyperthyroidism treated with ^{131}I only ($n=15$), (Eut: euthyroid; Hypo: hypothyroid; Hyper: hyperthyroid).

This difference in the time of treatment seemed to be mainly due to the influence of LiCO_3 on the ^{131}I effective half-life in the gland and on other aspects of thyroid function without affecting thyroid ^{131}I uptake [9–11, 17]. Thus, an increased radiation dose was delivered to the thyroid [13], which led to a higher degree of gland destruction, earlier suc-

cessful response of RIT, and hypothyroidism. The cited studies [12–14, 25] included patients with a recent onset of GHT, except of the study of Martin et al. (2012). The important finding of our study was that not all patients were hypothyroid at the end of the study unlike treated control patients who did not receive lithium and all of whom were hypothyroid at 9 months (Figure 2).

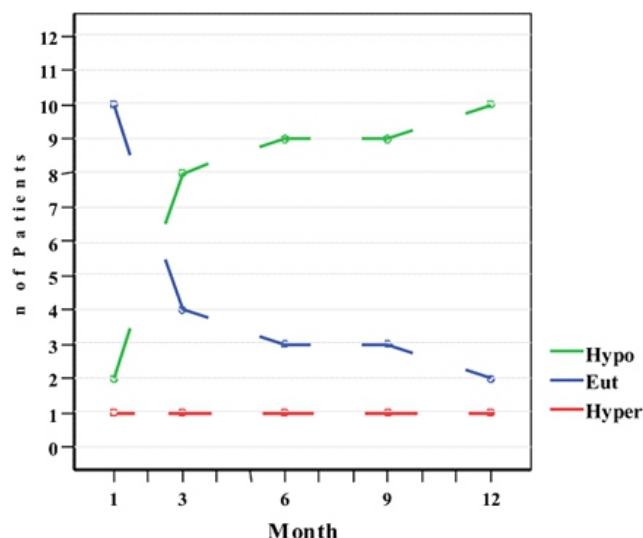


Figure 2. Radioiodine therapy response during 12 months follow-up period in patients with Graves' hyperthyroidism treated with ^{131}I combined with LiCO_3 ($n=13$), (Eut: euthyroid; Hypo: hypothyroid; Hyper: hyperthyroid).

However, other authors showed no significant effect of LiCO_3 on the therapeutic given together with ^{131}I [16, 23]. No significant differences existed in the cure rate and in the urinary excretion of ^{131}I , between patients treated and not treated by LiCO_3 [15]. Ahmed et al. (2006) in a small number of patients showed an excellent cure rate in the LiCO_3 group and in the non- LiCO_3 group (4.50% vs. 10.5% were not cured, respectively) at least six months after treatment.

The above results of ours also showed in patients treated only with ^{131}I a significant increase in serum total thyroxine (Tt_4), and free thyroxine (FT_4) and decrease of TSH level. This phenomenon which usually occurs several days after ^{131}I treatment started as a result of gland irradiation was absent in patients treated with ^{131}I in combination by LiCO_3 . The early protective effect of LiCO_3 in GHT patients on the release of thyroid hormones from the gland after ATD withdrawal has also been reported either LiCO_3 was given with [13, 14, 17] or without ^{131}I treatment [20, 21]. In patients with newly diagnosed GHT treated with LiCO_3 (900 mg/d for 12 days), plus ^{131}I after ATD withdrawal Bogazzi et al. (2010) showed that serum FT_4 concentrations remained normal which is in accordance with our study.

They also reported that in patients treated with ^{131}I alone, serum FT_4 concentrations increased, reaching a peak between 3 and 5 days after treatment ($K<0.0001$ for both days), which is also in accordance with our study. Carlson et al. (1973) reported a 26.0%–45.0% delay of T_4 disappearance slope following a short-course of LiCO_3 treatment in GHT patients not treated with ^{131}I , and no change in the T_4 disappearance slope in euthyroid individuals.

We did not record any toxic effects after LiCO_3 treatment. It seemed that a daily dose of 900mg for a short-term inducing a low serum level (0.400-0.990mmol/L) in patients with normal renal function and serum electrolytes levels was safe. There are reports on LiCO_3 side effects with a low dose of 400-900mg/d when the drug was given for a short-term together with ^{131}I after ATD withdrawal [12, 13, 16]. In the study of Turner et al. (1976) and Bogazzi et al. (2010), no significant side effects were experienced by any of their patients. To our knowledge, only one study has analyzed the impact of LiCO_3 in combination with ^{131}I as for thyroid-associated ophthalmopathy in GD and also concluded that ophthalmopathy did not worsen during 12 months of treatment [12].

In conclusion, the above indicate that in GHT patients short-term treatment with LiCO_3 as adjunct to ^{131}I improves the efficacy of RIT, prevents transient exacerbation of hyperthyroidism after ^{131}I treatment and also prevents early induction of hypothyroidism. The use of LiCO_3 for 7 days is safe and when applied with ^{131}I does not worsen ophthalmopathy during 12 months after treatment.

The authors declare that they have no conflicts of interest.

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