

University of Groningen

The influence of lithiumcarbonate on the hypothalamic-pituitary-thyroid axis. Studies in patients with affective disorders, thrototoxicosis and hypothyroidism

?

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
1977

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
? (1977). The influence of lithiumcarbonate on the hypothalamic-pituitary-thyroid axis. Studies in patients with affective disorders, thrototoxicosis and hypothyroidism. s.n.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

In 1968 it was shown by Schou that longterm lithium therapy in psychiatric patients may cause hypothyroidism or goiter. Lithium is frequently used for manic-depressive diseases (i.e. bipolar depressions) and recurrent (i.e. unipolar) depressions, further to be called 'affective disorders'. The influence of lithium-carbonate on the function of the hypothalamic-pituitary-thyroid axis in patients with affective disorders, thyrotoxicosis and hypothyroidism is discussed in this thesis.

The aim of the study was:

1. To establish the frequency and nature of lithium induced changes on the function of the hypothalamic-pituitary-thyroid axis.
2. To explore the possibility of detecting early dysfunction of the thyroid in patients on longterm lithiumcarbonate.
3. To answer the question, whether there is a place for clinical use of lithium-therapy in the treatment of thyrotoxicosis.

The survey of the literature in chapter I starts with a description of the discovery and use of lithium. Attention is paid to its pharmacology. The possible mode of action in patients with affective disorders is discussed: lithium can affect synaptic transmission, nerve excitation, and neuronal metabolism. However, it is not clear, whether these effects are produced by alterations of ion transport or distribution, by inhibition of adenylcyclase mediated responses or by more direct interference with neuronal metabolism. Common side effects and complications, as well as toxicology and treatment associated with longterm lithium therapy, are described. The thyroid physiology is reviewed and the possible mode of action on the thyroid homeostasis is considered.

The groups of patients studied and the methods used for evaluation of the function of the hypothalamic-pituitary-thyroid axis are presented in chapter II. The patients were divided in three categories (A, B and C). The categories are subdivided.

Category A consists of clinically euthyroid patients with affective disorders on maintenance lithiumcarbonate. TRH tests were performed before, and during 2 and 6 weeks after starting lithium therapy in 7 patients (category A-1), before and at 3-monthly intervals during therapy, for a longer period of time in 13 patients (category A-2), and finally during lithium treatment and after 2, 4 and 6 weeks after discontinuation of the medication (category A-3). Category A-4, consisting of all patients of the categories A-1, A-2, A-3 and some others, shows the incidence of hypothyroidism, goiter or both conditions in 46 patients, who were seen in a period of 28 months. Thirty of these patients, who were seen at 3-monthly intervals were divided in two subgroups A-4a (22 patients)

and A-4b (8 patients), according to a normal or raised basal TSH level, respectively.

The second group studied (category B) consists of 26 thyrotoxic patients, of whom four were contaminated with exogenous iodine (category B-2).

Seven patients with hypothyroidism, of whom one patient was athyreotic, form category C.

The first part of chapter III deals with the results of TRH tests before, during and after longterm lithium therapy in patients with affective disorders (category A-1, A-2 and A-3). It appears that lithiumcarbonate, at serum lithium levels varying from 0,4 to 1,2 mEq/l, has a rapid inhibitory effect on thyroid hormone release. This leads to an initial decrease of free T₄ (FT₄F) and free T₃ (FT₃F), calculated according to Hamada (1970). Meanwhile a new equilibrium is set to maintain thyroid homeostasis, as is expressed by a permanent increased TSH response to TRH and often by a raised basal TSH, resulting in practically normal thyroid hormone levels.

The second part of this chapter reports that two (4.4 %) of the 46 patients (category A-4) on maintenance lithium therapy, developed a goiter, four (8.7 %) became clinically hypothyroid, whereas eleven (23.9 %) had a transient or permanent increase in basal TSH level. The group with elevated basal TSH levels (A-4b) showed a remarkably high incidence of thyroid antibodies (50 %). It appears that individuals on longterm lithium therapy with a so-called 'low thyroid reserve' are predestined to develop hypothyroidism. History, increased basal TSH levels, the presence of antibodies and later on, the clinical picture have to draw our attention to the possibility of imminent hypothyroidism.

The effect of lithium on the hypothalamic-pituitary-thyroid axis is reversible; discontinuation of therapy normalizes the TSH response within 6 weeks. The induced changes seem to be proportional to the serum lithium levels, as can be seen from two case histories. It is concluded that a thorough clinical and laboratory investigation should precede initiation of lithium therapy and should be pursued throughout the course of the treatment.

The results of the treatment with lithiumcarbonate of thyrotoxic patients (category B) is the subject of chapter IV. It appears that lithium, at serum lithium levels of 0,8 mEq/l, almost completely blocks the thyroidal hormone release during the first 6 days of therapy. However, the TSH response to TRH does not normalize. Four thyrotoxic patients were prepared with lithiumcarbonate and underwent subtotal thyroidectomy without complications.

Five patients were treated with maintenance lithium therapy. After initial euthyroidism, four relapsed. This is probably due to an escape phenomenon, caused by thyroidal iodine pooling. One patient remained clinically euthyroid for over a year. However his ¹³¹I uptake had normalized.

The result of lithium treatment in patients with thyrotoxicosis and iodine contamination, caused by contrast mediums, was less favourable. However, combination treatment with thionamides, which inhibits the iodine organification, may prove to be useful by preventing iodine pooling.

¹³¹I uptake tests before and during lithium therapy show that iodine is retained

by the thyroid. This means that lithiumcarbonate might be a useful adjunct to ^{131}I therapy, particularly in case of metastatic thyroid malignancy, to diminish the total body radiation.

In conclusion, lithiumcarbonate seems to be useful to restore euthyroidism rapidly, although the side effects have to be taken into consideration. In contrast to iodine, lithium therapy does not interfere with diagnostic measurements of thyroid function, which is an advantage.

Chapter V describes the influence of lithium in patients with hypothyroidism (category C) studied, to derive additional information concerning the action of lithium on the hypothalamic-pituitary axis. The best approach is to perform a study in a totally thyroidectomized individual. An athyreotic patient, who had not been taking his replacement therapy for at least 3 months, was treated with lithiumcarbonate for a week. At serum lithium levels of 0,7 mEq/l a direct negative effect of lithium on the TSH secretion is documented.

Subsequently, a group of 6 patients with hypothyroidism was studied. The results show that as long as lithium is able to decrease thyroid hormone production, one cannot exclude its indirect positive influence on the TSH production by the pituitary. Thus, in hypothyroid patients with residual thyroid function, the thyroidal hormone release inhibition by lithium provides an indirect positive effect, which obscures lithium's direct negative effect on TSH secretion.

Some years ago lithiumsalts became popular temporarily, as a salt substitute in sodium restricted diets. Soon, however, because of reported toxic side effects their use was stopped abruptly. Nowadays, lithiumcarbonate is frequently used in some groups of psychiatric patients. Better knowledge of lithium's properties enables us to prevent undesirable side effects. Moreover, one of these side effects can be useful in the treatment of patients with thyroid diseases, e.g. thyrotoxicosis and thyroid malignancy.