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Use of lithium in the treatment of thyrotoxicosis

鋰治療甲狀腺功能亢進

Objectives. To evaluate the efficacy and safety of lithium in the treatment of thyrotoxicosis, and to study the dose and serum levels at which therapeutic response occurs.

Design. Retrospective study.

Setting. Thyroid clinic of a regional hospital in Hong Kong.

Patients. Thirteen patients with thyrotoxicosis pending therapy with radioiodine or surgery, in whom thionamides were contra-indicated due to adverse reactions or failure of treatment.

Main outcome measures. Free thyroxine levels, time to euthyroidism, and side-effects of lithium.

Results. A satisfactory response, defined as a fall by 40% or more in free thyroxine levels and clinical improvement, was achieved in eight patients within 1 to 2 weeks of lithium therapy. In four others, response occurred in 3 to 5 weeks. Response was slow and inadequate in one patient due to 'escape'. The median dosage of lithium was 750 mg daily, with a range of 500 to 1500 mg daily. The median serum lithium level was 0.63 mmol/L. Lithium toxicity was observed in one patient.

Conclusions. A relatively low dose of lithium offers a safe and effective alternative means of controlling thyrotoxicosis in patients who cannot tolerate or do not respond to thionamides.

目的：評估鋰對治療甲狀腺功能亢進是否有效和安全，並研究能達療效所需的劑量和血清水平。

設計：回顧研究。

安排：本港一所地區醫院的甲狀腺診所。

患者：13 名正等候以放射性碘或施手術治療甲狀腺功能亢進的病人。他們對硫醯胺類治療有不良反應，或對此藥沒有療效反應。

主要結果測量：游離甲狀腺素水平、甲狀腺功能回復正常所需時間、鋰治療的副作用。

結果：有8名病人對鋰治療反應滿意，他們均在一至兩星期內游離甲狀腺素水平減少了 40% 或以上。另 4 名病人則在治療後三至五星期內獲得效果。最後一名病人對鋰治療反應緩慢。病人的每日鋰用量介乎 500 至 1500 mg，中位數為 750 mg。而血清鋰水平中位數為 0.63 mmol/L。一名病人出現鋰中毒。

結論：如果病人不能接受硫醯胺類治療，或對硫醯胺類治療沒有療效反應，低劑量的鋰治療是控制甲狀腺功能亢進的另一個安全有效的治療方法。

Key words:
Graves' disease;
Lithium;
Thyrotoxicosis;
Thyroxine

關鍵詞：
葛瑞芙氏症；
鋰；
甲狀腺功能亢進；
甲狀腺素

Hong Kong Med J 2006;12:254-9

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Introduction

Medical treatment is often used in the management of thyrotoxicosis due to Graves' disease, as the only treatment modality for a first episode of Graves' disease, or to decrease high thyroxine (T4) levels and reduce the risk of thyroid storm prior to radioiodine or surgery. Thionamides, for instance, propylthiouracil (PTU) and carbimazole (CBZ), are often prescribed and are generally safe and effective, although a few patients may develop serious side-effects and require alternative drugs. The choice of drugs in patients intolerant or unresponsive to thionamides is nonetheless limited. Iodide compounds can be effective, but will interfere with subsequent uptake of radioiodine. Perchlorate and thiocyanate are often not sufficiently effective, and serious side-effects such as irreversible aplastic anaemia[1] and methaemoglobinaemia have curtailed their

Table 1. Clinical details of patients treated with lithium

Patient No.	Age (years)/sex	Contra-indications to thionamides or failure of thionamide treatment*	Complications of thyrotoxicosis	Co-morbidity
1	33/F	CBZ-induced agranulocytosis, complicated by pseudomonas and staphylococcus septicaemia and oral and oesophageal candidiasis	Thyroid storm	-
2	49/F	CBZ-induced agranulocytosis and oral candidiasis	Atrial fibrillation	Diabetes mellitus
3	32/M	PTU-induced agranulocytosis	Periodic paralysis	-
4	18/F	PTU-induced neutropenia	-	-
5	66/M	TPZ- and PTU-induced neutropenia	-	-
6	28/M	Severe PTU-induced skin rash	Periodic paralysis	-
7	20/F	Severe PTU- and CBZ-induced skin rash	-	-
8	17/F	Persistent severe thyrotoxicosis despite high doses of PTU and potassium perchlorate	-	-
9	27/M	PTU-induced neutropenia	Graves' ophthalmopathy	Asthma, allergic rhinitis
10	30/F	CBZ-induced agranulocytosis	-	β-Thalassaemia trait
11	55/F	PTU-related hepatitis	-	Diabetes mellitus
12	37/F	CBZ-induced agranulocytosis	-	-
13	34/F	CBZ-induced agranulocytosis PTU-induced angioedema	Graves' ophthalmopathy	-

* CBZ denotes carbimazole, PTU propylthiouracil, and TPZ tapazole

acceptance. Lithium is known to affect thyroid hormone release and synthesis and its use to treat thyrotoxicosis was reported in the 1970s.[2-6] Although lithium has a narrow therapeutic index, it appears safe as long as serum levels are closely monitored. Moreover, as it is a common medication for the treatment of bipolar disorders, experience with this drug is much more extensive than with perchlorate or thiocyanate. We therefore decided to use lithium in our thyroid clinic for the treatment of thyrotoxicosis in selected patients (not responding to thionamides or in whom they were contra-indicated) and report our experience.

Methods

This was a retrospective review of patients treated with lithium for thyrotoxicosis in a regional hospital in Hong Kong from June 1996 to December 2004. Around 800 new cases of thyrotoxicosis are referred to our thyroid clinic each year. Our practice protocol for Graves' disease states that "lithium therapy may be considered for patients who are clinically and biochemically thyrotoxic AND either (i) thionamides are contra-indicated due to development of significant side-effects such as agranulocytosis or severe skin rash, or (ii) they are unresponsive to an adequate trial of thionamides". In accordance with our protocol, 13 patients were prescribed lithium during this period. In all cases, the purpose of the lithium was to better prepare the patient for the definitive treatment, by ameliorating the degree of thyrotoxicosis, whenever thionamide treatment had to be discontinued due to severe side-effects or lack of efficacy. Beta-blockers were continued unless contra-indicated. Subjects were informed of the potential risks and benefits of taking lithium therapy and verbal consent obtained before initiating therapy with lithium carbonate 250 mg thrice daily. All patients were closely observed for the clinical progress of their thyrotoxicosis and for possible side-effects or toxicity from lithium treatment. Serum free thyroxine (fT4) and lithium levels were also monitored. Trough lithium level was checked on day 4 after commencement, followed by periodic monitoring. Lithium level was monitored by an ion selective electrode using a Nova electrolyte analyser (Nova Biomedical, Waltham [MA], US). The between-batch imprecision of this assay was less than 5% at therapeutic levels of lithium.

Results

From June 1996 to December 2004, 13 patients fulfilled the treatment criteria. Their ages ranged from 17 to 66 years, with a median of 32 years and their demographic and clinical details are presented in Table 1. Lithium was administered to control thyrotoxicosis in 12 patients because of intolerance to thionamides, mainly severe neutropenia or agranulocytosis. In one patient (No. 8) it was used to treat thyrotoxicosis, which was uncontrolled despite high-dose PTU (800-1200 mg/day) for a month together with potassium perchlorate treatment. Patient No. 9 had received radioiodine therapy 1 year earlier, whereas none of the others had received prior radioiodine or undergone thyroid surgery. For each patient, the dosages of lithium therapy, its duration, respective serum levels and its timing in relation to their definitive treatment are listed in Table 2. One patient (No. 5) received radioiodine 7 days before lithium was initiated. Ten others received radioiodine 7 to 30 days after initiation of lithium. Radioiodine treatment was given at a dose of 400 MBq to all patients except No. 6, who was given 370 MBq. One patient (No. 8) underwent subtotal thyroidectomy on day 16 and another (No. 13) underwent total thyroidectomy after 5 months of unsatisfactory response to medical treatment. Two patients (Nos. 5 and 11) with persistent hyperthyroidism were given a second dose of radioiodine after 3.5 and 6 months, respectively. Patients Nos. 10 and 11 defaulted from follow-up after achieving euthyroidism at 20 and 34 weeks, respectively. The fT4 levels prevailing after lithium therapy are shown in Table 3. In eight patients (Nos. 1, 4, 5, 6, 8, 10,

Table 2. Treatment with lithium and radioiodine therapy (RAI)/surgery in patients intolerant/unresponsive to thionamides

Patient No.	Daily dose of lithium (mg)	Duration of lithium therapy (days)	Serum lithium level* (mmol/L)	Type of definitive treatment and day of administration†
1	500-1000	20	0.47	RAI on day 11
2	750	36	0.50	RAI on day 13
3	750	56	0.60	RAI on day 8
4	750	35	0.58/0.48	RAI on day 21
5	750	56	0.80/0.90	RAI on day -7 and day 101
6	750-1500	14	0.70	RAI on day 7
7	750	48	0.63	RAI on day 8
8	750	17	0.40	Subtotal thyroidectomy on day 16
9	750-1000	37	0.30/0.54/0.60	RAI on day 20
10	500-750	63	0.80/0.80	RAI on day 30
11	750	12	0.80	RAI on day 12 and day 188
12	500-750	17	1.60/3.40	RAI on day 23
13	750-1000	155	0.30/0.50/1.00/0.70/0.60/0.80	Total thyroidectomy on day 155
Median	750	36	0.63	
Range	500-1500	12-155	0.30-3.40	

* Therapeutic serum lithium level: 0.60-1.20 mmol/L
† Day 0 is taken as the day on which lithium treatment was started

11, and 12), a rapid decline was observed, ranging from 44.5 to 82.3% of their baseline values within 2 weeks of treatment. Among this group of rapid responders, four patients (No. 1, 5, 6, and 11) received radioiodine on days 11, -7, 7, and 12 respectively in relation to commencing lithium. Three others (Nos. 4, 10, and 12) received radioiodine on day 21, 30, and 23 after introduction of lithium, when their fT4 levels had already decreased by more than 73%, 57%, and 82% respectively. Similarly, for patient No. 8, the decrease in fT4 of 63% could be attributed to lithium therapy alone, since subtotal thyroidectomy was only performed on day 16 (Table 2). In four other patients (Nos. 2, 3, 7, and 9), a slower decline in fT4 level was observed at 3 to 5 weeks after initiation of lithium (corresponding to 1 to 3 weeks after radioiodine). Overall, after lithium therapy there was a mean reduction in fT4 levels of 27.1% after 1 week and 43.2% after 2 weeks. The median serum lithium level was 0.63 mmol/L. The duration of lithium therapy ranged from 12 to 155 days. Lithium was stopped when the patient's thyrotoxicosis was under stable control. No patient showed a relapse of thyrotoxicosis after ceasing lithium, possibly because definitive therapy had also been given. The only patient (No. 13) not responding satisfactorily to lithium therapy had a huge goitre, Graves' ophthalmopathy, and florid thyrotoxicosis with fT4 levels greater than 100 pmol/L. Her fT4 level declined by 48.3% after 8 weeks of lithium treatment, but started to rebound after 12 to 16 weeks post-starting lithium and increased from 55.0 to 71.5 pmol/L from week 16 to week 20. Total thyroidectomy was performed under dexamethasone cover and beta-blockade after 5 months of medical treatment.

One patient (No.12) developed lithium toxicity. She presented with nausea, vomiting, tremor, cerebellar signs, and mental obtundation 17 days after lithium was initiated at a daily dose of 750 mg. Computed tomographic brain scan and cerebrospinal fluid examination were unremarkable. Her lithium levels were in the toxic range (Table 2), despite having normal renal function and not

Table 3. Free thyroxine (fT4) levels after lithium therapy and outcomes of the patients after definitive treatment of thyrotoxicosis

Patient No.	fT4 levels in pmol/L at week 0-8 after lithium therapy*					
	0	1	2	3	4	5
1	120.1	114.2 (4.9%)	66.6 (44.5%)	37.1 (69.1%)	-	-
2	92.0	65.1 (29.2%)	78.5 (14.7%)	73.2 (20.4%)	37.1 (59.7%)	33.8 (63.2%)
3	36.6	31.0 (15.3%)	31.0 (15.3%)	30.0 (18.0%)	19.5 (46.7%)	-
4	140.3	84.9 (39.5%)	48.8 (65.2%)	38.3 (72.7%)	52.5 (62.6%)	37.4 (73.3%)
5	79.9	38.0 (52.4%)	38.2 (52.2%)	-	-	-
6	51.7	26.9 (48.0%)	17.4 (66.3%)	-	-	-
7	131.7	148.8 (+13.0%)	105.5 (19.9%)	58.1 (55.9%)	-	-
8	>155†	91.6 (40.9%)	57.5 (62.9%)	-	-	-
9	27.6	37.3 (+35.1%)	-	-	-	15.6 (43.5%)
10	>155†	70.3 (54.6%)	95.6 (38.3%)	73.6 (52.5%)	66.3 (57.2%)	-
11	108.8	66.4 (39.0%)	47.2 (56.6%)	-	-	-
12	103.0	29.4 (71.4%)	18.2 (82.3%)	-	-	-
13	>100†	94.8 (5.2%)	>100.0 (0%)	87.3 (12.7%)	-	71.5 (28.5%)
Mean % reduction in fT4	-	27.1%	43.2%	43.0%	56.6%	52.1%

* Week 0 is taken as the week in which lithium treatment was started; % reduction is shown in brackets
† fT4>155 pmol/L and fT4>100 pmol/L were the highest fT4 values measured by our assays in two different periods during the 8.5-year study period. Values of >155 pmol/L or >100 pmol/L are taken as 155 pmol/L or 100 pmol/L, respectively in calculating the % reduction in fT4 with lithium treatment. Normal ranges for fT4 were 11.5-23.2 pmol/L and 12.0-22.0 pmol/L, respectively in the two time periods

taking drugs that might have potentiated lithium toxicity. She gradually recovered after lithium was discontinued and having haemodialysis.

Discussion

Thionamides are generally the first drugs of choice in the treatment of hyperthyroidism. However, they are associated with serious side-effects[7] such as hepatitis and cholestatic jaundice, agranulocytosis, anti-neutrophil cytoplasmic antibody–positive vasculitis, polyarteritis nodosa, hypoprothrombinaemia, disseminated intravascular coagulation, lupus-like syndrome, aplastic anaemia, and glomerulonephritis. Cross-reactivity between CBZ and PTU has been reported to be up to 50%.[8] Replacing CBZ with PTU or vice versa in patients developing either of these serious adverse reactions therefore poses a risk. In Graves' disease patients who develop serious reactions to thionamides or are unresponsive to high doses of thionamides, definitive treatment such as surgery or radioiodine is often indicated. Before these can be offered, it is safer to ameliorate the degree of thyrotoxicosis medically, to reduce the risk of thyrotoxic crisis that may be precipitated by the stress of surgery or post-radioiodine thyroiditis.[9,10]

Lithium is concentrated by the thyroid gland and has multiple actions that resemble those of iodine. It is taken up avidly by thyroid cells and blocks thyroid hormone release from thyroglobulin,[11] which inhibits adenylate cyclase and prevents thyroid-stimulating hormone (TSH) or thyroid stimulating antibody from activating thyroid cells via the TSH receptor.[12] It may also affect thyroid hormone synthesis. Thyroid dysfunction is a well-known complication when lithium is used to treat bipolar disorder and goitre has been reported to develop in 50% of patients.[13] Lithium is a well-recognised cause of hypothyroidism but has also, albeit less commonly, been associated with hyperthyroidism.[14,15] The exact mechanisms by which it leads to thyroid dysfunction have not been ascertained, but lithium-related autoimmune thyroiditis seems to play a role in some patients.

The use of lithium as an anti-thyroid drug was first reported by several groups about three decades ago.[2-6] Lazarus et al[5] for example reported its use for 6 months as the only anti-thyroid drug in 12 patients with Graves' disease who relapsed following treatment with conventional anti-thyroid drugs, surgery, or radioiodine. The dose of lithium ranged from 800 to 1200 mg daily, resulting in serum levels of 0.5 to 1.5 mmol/L. One of their patients withdrew after 3 weeks due to 'a sense of depersonalisation', nausea, and tremor. Eight of the remaining 11 patients became clinically euthyroid 2 weeks after lithium was commenced; serum T4 and triiodothyronine (T3) decreased by a mean of 35%. The other three became clinically euthyroid 4 to 6 weeks after starting lithium. Euthyroidism was maintained for 6 months, and none developed hypothyroidism, though seven experienced a relapse of thyrotoxicosis 1 to 4 weeks after stopping it. Other studies reported a decrease of T4 by 21 to 30% in 6 days[2] and 40% in 4 days.[3]

In 1976, Turner et al[6] reported using lithium as an adjunct to radioiodine in the treatment of thyrotoxicosis. It was given at a dose of 400 mg daily to 16 patients (from 1 week before to 1 week after radioiodine), and resulted in serum levels of 0.05 to 0.75 mmol/L (mean, 0.36 mmol/L). When compared with the control group, those treated with lithium showed a significantly greater 24 to 168-hour retention of radioactive iodine by the thyroid gland. The investigators concluded that low-dose lithium therapy increased retention of radioiodine, and could be a useful adjunct to radioiodine in patients with a rapid thyroidal iodine turnover, or in young patients in whom it is desirable to keep the total body-radiation dose to a minimum. More recently, an Italian randomised study reported their results in 110 patients with Graves' hyperthyroidism treated with radioiodine or radioiodine plus lithium.[16] Lithium was given at a dose of 900 mg/day for 6 days, starting on the day of

			Time to euthyroidism (weeks)	Time to hypothyroidism (weeks)
6	7	8		
-	-	-	5-9	9
-	-	-	9	34
7.5 (79.5%)	-	-	3-4	7
-	-	-	9-12	12
-	37.9 (52.6%)	-	17	208
-	-	-	1-2	20
23.6 (82.1%)	-	-	7	9
-	-	-	Immediately postoperative	3
-	-	-	5	9
-	33.6 (78.3%)	-	20	Defaulted follow-up after week 20
-	-	-	34 (after second-dose radioiodine)	Defaulted follow-up after week 36
-	-	-	2	13
-	-	51.7 (48.3%)	Immediately postoperative	Immediately postoperative
80.8%	65.5%	48.3%		

radioiodine administration. Patients with goitre size of 40 mL or smaller achieved similar cure rates with or without lithium, but the group given lithium achieved more rapid control of hyperthyroidism. Among patients with goitre sizes of more than 40 mL, only 25% of those given radioiodine plus lithium were hyperthyroid at 12 months of follow-up, in contrast to 60% among those treated with radioiodine alone.

The recommended dose of lithium is usually 900 to 1200 mg daily. Rapid complete absorption occurs within 6 to 8 hours, and a steady-state serum concentration is achieved in 4 days. Lithium is mainly renally excreted; the elimination rate tends to decrease with age, and when patients are dehydrated, or concurrently taking agents such as diuretics, angiotensin-converting enzyme inhibitors, or non-steroidal anti-inflammatory drugs. The therapeutic serum lithium concentration is quoted as 0.6 to 1.2 mmol/L.[17,18] Its documented adverse effects include central nervous system disturbance (confusion, blurring of vision, clumsiness, seizures, and coma) and arrhythmias (ventricular irritability, sinus node dysfunction, and sinoatrial block).[19,20] In addition, lithium is toxic to cells of the distal renal tubule and may cause nephrogenic diabetes insipidus. It is therefore considered mandatory to monitor serum lithium levels closely. Serious complications rarely occur unless serum lithium level exceed 1.5 mmol/L.[21] Because of the time lag before availability of laboratory results, continuous clinical monitoring is of utmost importance. Early symptoms of toxicity include diarrhoea, vomiting, loss of appetite, drowsiness, slurring of speech, polyuria, hand tremor, and muscle weakness. As demonstrated by patient No. 12, toxicity can develop in those prescribed therapeutic doses of lithium, and in the absence of risk factors that predispose to lithium toxicity. In view of these potential adverse effects and data showing that lithium has no advantage over thionamides in the treatment of thyrotoxicosis,[4] we believe it is only indicated in patients developing serious side-effects from the latter drugs or are unresponsive to adequate dosing with them. Although other investigators have reported that combination therapy of thionamides and lithium can accelerate the rate and extent of decrease in T4 and T3 levels,[22] we do not recommend such combinations as routine primary therapy for Graves' disease in view of the latter's narrow therapeutic index and the effectiveness of the former.

As high rates of relapse have been reported after discontinuation of lithium therapy,[5] definitive therapy such as radioiodine and surgery should be planned. The use of lithium is intended principally to better prepare thyrotoxic patients for definitive therapy. The possibility of 'escape' from the effects of lithium, as observed in patient No. 13, by 12 to 16 weeks of treatment, emphasises the importance of early definitive treatment.

Because of the stringent criteria adopted in our practice protocol, lithium therapy was prescribed to only a few patients. Thus of the more than 800 new referrals each year to our thyroid clinic, only 13 patients qualified for lithium over a period of 8.5 years. A satisfactory response, defined arbitrarily as a fall by 40% or more in fT4 levels and clinical improvement, was achieved in eight patients within 1 to 2 weeks. Since four of these patients (No. 4, 8, 10, and 12) were not given definitive therapy until fT4 levels had already decreased, we believe this magnitude of response confirms that lithium treatment is effective by itself. In the other four patients, fT4 levels decreased by 50% or more within 1 week of radioiodine (No. 1, 5, 6, and 11). Such a rapid response is unusual in patients given radioiodine alone, which suggests that lithium must have played a role. In the four patients (No. 2, 3, 7, and 9) who had a reduction in fT4 by 40% or more within 1 to 3 weeks of radioiodine, it is difficult to differentiate the effect of radioiodine from that of lithium.

The dose of lithium used was relatively small. Most patients appeared to respond to 750 mg daily. Although the therapeutic serum level for bipolar disorders is quoted to be between 0.6 and 1.2 mmol/L, lower levels (0.3 to 0.7 mmol/L) seemed to elicit a rapid and satisfactory control of thyrotoxicosis in most patients. One patient (No. 8) did not respond to high doses of PTU and potassium perchlorate. This patient had a history of taking herbal medicine, as is common among our population. Some of the herbs were seaweeds with a high iodine content, which may have interfered with the effectiveness of the anti-thyroid drugs. Although we attempted to improve the efficacy of such drugs by adding potassium perchlorate to discharge the high intrathyroidal iodine store, it was not effective. This patient responded well to lithium therapy, with a decrease in fT4 from over 155 pmol/L to 57.5 pmol/L within 2 weeks, allowing subtotal thyroidectomy to be performed safely 16 days later. The mechanism(s) of action of lithium in this clinical scenario remain uncertain, but we speculate that displacement of intrathyroidal iodine by lithium may have played a role.

In conclusion, our experience confirms that lithium is effective in the treatment of thyrotoxicosis. It is also well tolerated when serum levels are kept below 1.0 mmol/L. The usual dose is 250 mg thrice daily, but depending on serum levels, it may be increased to 500 mg thrice daily. Close observation for lithium toxicity and therapeutic drug monitoring are considered mandatory. In patients who develop serious side-effects due to thionamides or who do not respond to these drugs, lithium therapy can be used as an effective interim measure before undertaking definitive therapy.

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