

Successful Oral Levothyroxine Desensitization in a Patient with Severe Hypothyroidism Post Radioactive Iodine Therapy: A Case Report

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Abstract

Levothyroxine remains the standard therapy for patients with hypothyroidism worldwide. Levothyroxine allergy is rarely seen and alternative therapies are less efficacious and scarcely available. The use of liothyronine (LT3) monotherapy is less favoured due to its short half-life and unpredictable pharmacological profile. We report a 59-year-old male with a hypersensitivity reaction to levothyroxine who was successfully desensitized with oral levothyroxine within a day using a 14-step protocol.

Key words: levothyroxine, hypersensitivity, hypothyroidism, desensitization

INTRODUCTION

Hypothyroidism is common post radioactive iodine (RAI) therapy. The incidence of hypothyroidism within a year post RAI therapy in Malaysia is 32.9%.¹ The standard treatment for hypothyroidism is oral levothyroxine (LT4). The majority of patients tolerate levothyroxine well without any adverse effects as it is identical to the molecule produced by the body.² Unfortunately, patients who develop an allergy towards levothyroxine have no other substitute compound that is as efficacious to alleviate the hypothyroid symptoms.

The common practice of switching to other commercially available preparations of levothyroxine with different excipients will usually resolve the issue.² However, if this strategy fails, desensitization to levothyroxine should be considered.

CASE

A 59-year-old male with Graves' disease who was rendered hypothyroid post radioactive iodine (RAI) therapy, reported he was unwell four days after commencement of levothyroxine 50 mcg daily. Free thyroxine (FT4) level was 3.9 pmol/L (normal range 11.8-23.2 pmol/L) and thyrotropin (TSH) level was 41.26 mU/L (normal range 0.35-5.50 mU/L). His comorbidities include hypertension and diabetes with no history of drug allergies. Within four days of levothyroxine initiation, he developed facial edema, abdominal distension, swelling of distal extremities and dyspnoea. He continued taking the medication but due to worsening symptoms, he withheld it two weeks prior to the clinic consultation. During the clinic review, his previous symptoms had completely resolved but he was clinically hypothyroid. He had weight gain of 9 kg (97 kg to 106 kg) and constipation. He was switched

Table 1. Oral levothyroxine desensitization protocol

Steps	Stock Solution	Cumulative Time (min)	Dose (mcg)	Volume (mL)	Cumulative Dose
1	1	30	0.01	0.1	0.01
2	1	60	0.02	0.2	0.03
3	1	90	0.04	0.4	0.07
4	1	120	0.08	0.8	0.15
5	1	150	0.16	1.6	0.31
6	1	180	0.32	3.2	0.63
7	2	210	0.64	6.4	1.27
8	2	240	1.28	12.8	2.55
9	2	270	2.56	25.6	5.11
10	2	300	5.12	51.2	10.23
11	3	330	10.00	5.0	20.23
12	3	360	20.00	10.0	40.23
13	3	390	30.00	15.0	70.23
14	3	420	40.00	20.0	110.23

adapted from Fevzi et al.³

to another levothyroxine preparation with different excipients. The same symptoms recurred and he presented to the emergency department the next day.

On examination, his vital signs were stable with a blood pressure of 113/74 mm Hg, heart rate of 72 beats per minute, oxygen saturation of 100% on room air. He was afebrile. He had mild facial puffiness and swelling of his fingers. Jugular venous pressure was not elevated and cardiovascular examination was unremarkable. He was not tachypnoeic and his lung examination revealed clear lung fields.

Admission biochemistry revealed a normal full blood count with readings of haemoglobin 13.0 g/dL (normal range 13.2-16.6 g/dL), white blood cells $7.63 \times 10^9/L$ (normal range $4.0-11.0 \times 10^9/L$), platelets $137 \times 10^9/L$ (normal range $135-317 \times 10^9/L$) and eosinophils 2.5% (normal range 1-4%). His renal function revealed an acute kidney injury profile where the urea was 6.3 mmol/L (normal range 2.5-10.7 mmol/L) and creatinine 153 $\mu\text{mol/L}$ (normal range 62-106 $\mu\text{mol/L}$) (baseline 92 $\mu\text{mol/L}$). His creatine kinase was markedly elevated at 3085 u/L (normal range 34-145 u/L). This coincided with his severe hypothyroidism where his free T4 was $<1.3 \text{ pmol/L}$ (normal range 11.8-23.2 pmol/L) and thyrotropin (TSH) level was 62.05 mU/L (normal range 0.35-5.50 mU/L).

He was initiated with intravenous levothyroxine at a daily dose of 100 mcg for four consecutive days as he was severely hypothyroid. This was done with an initial test dose of 1 mcg administered as a slow bolus over five minutes, followed by the remaining dose given over another five minutes with continuous cardiac and vital sign monitoring. He had no immediate or delayed hypersensitivity reaction to the intravenous preparation.

Oral levothyroxine desensitization was commenced on the second day of admission. The dosage was designed based on a previously reported protocol (Table 2).³ After obtaining a written consent from the patient, oral levothyroxine was given at an initial dose of 0.01 mcg and this was doubled every 30 minutes for seven hours until a cumulative dose of 110 mcg was reached (Table 2). He was put on continuous cardiac and vital sign monitoring throughout the desensitization process and emergency medications of parenteral hydrocortisone, chlorpheniramine and adrenaline were prepared at bedside in case he developed any allergic reaction. The desensitization of levothyroxine was successful without signs or symptoms of allergy. He was discharged well five days after admission with 100 mcg of oral levothyroxine.

Table 2. Oral Levothyroxine Stock Solution Preparation

Name of Medication: Levothyroxine			
Stock Solution	Volume Per Stock Solution (mL)	Concentration (mcg/ml)	Total Dose Per Stock Solution (mcg)
1	10	0.1	1
2	100	0.1	10
3	50	2.0	100

Target dose (mcg): 110.23

DISCUSSION

Hypersensitivity reaction to levothyroxine can present as a type 1 (immediate) or type 4 (delayed) hypersensitivity reaction.⁴ The IgE mediated immediate reaction most commonly manifests as urticarial rash within minutes to hours, whereas the T-cell mediated delayed reaction usually occurs several days to weeks after exposure. Other hypersensitivity reactions to levothyroxine include angioedema, eczematiform skin eruptions, and pruritus.⁵ To date, there is limited information on whether levothyroxine hypersensitivity reaction is IgE-mediated or non-Ig-E-mediated.⁶ It is recommended to perform skin testing but this was only reported in certain cases. Unfortunately, skin testing was not available in our setting. We believe that our patient developed type 1 hypersensitivity reaction as his allergic symptoms occurred on the day where he consumed the oral levothyroxine and similar reactions occurred almost immediately with the change to the other oral levothyroxine preparation.

Most patients with hypersensitivity reaction tolerated an alternative thyroxine preparation without further reaction, supporting the theory that the allergy is likely due to the excipients or fillers rather than the thyroid hormone itself.⁵ Thus, a trial of switching the patient to an alternative levothyroxine preparation is usually done. This was not successful with our patient and the gel capsule formulation which has the least excipients was not available locally. However, our patient was able to tolerate the intravenous preparation of levothyroxine, suggesting that it was the excipients or fillers that most likely triggered the atypical hypersensitivity reaction that resolved upon stopping the oral levothyroxine and recurred upon reintroduction.

Therapies such as desiccated thyroid extracts (DTE) from animal thyroid glands and oral liothyronine (T3) are not recommended as substitutes for levothyroxine therapy.² The use of these formulations as monotherapy or in combination with levothyroxine remains an ongoing debate. This is due to the short half-life of liothyronine (T3) and the non-standardized doses of the desiccated thyroid hormone.²

While compounded thyroid hormone has been suggested as a reasonable alternative for patients with levothyroxine allergy,² the cost is high and their formulations are not standardized, resulting in occurrences of both hypothyroidism and hyperthyroidism that are difficult to predict.⁷ Thus, if patients are unable to tolerate the alternative preparations of levothyroxine with different excipients, desensitization should be performed in an inpatient setting.

Desensitization is a procedure that alters the immune response to a drug and results in temporary tolerance, allowing the patient with a drug hypersensitivity reaction to receive an uninterrupted course of the medication safely.⁸ Once the medication is discontinued or if treatment is interrupted for a sufficient period, the patient's hypersensitivity to the medication returns. Successful levothyroxine desensitization was mostly reported in IgE mediated drug hypersensitivity reactions with only one case involving delayed hypersensitivity reaction.⁹

Successful desensitization was achieved within 1-2 days in most cases.^{3,10} These patients remained asymptomatic without further allergic reactions.

CONCLUSION

With the lack of alternative option to treat hypothyroidism, patients who develop hypersensitivity reaction to oral levothyroxine should be desensitized using a step-wise protocol if they are unable to tolerate alternative preparations of levothyroxine. This should be performed as soon as possible to prevent complications of untreated hypothyroidism that can be life threatening.

Ethical Consideration

Patient consent was obtained before submission of the manuscript.

Statement of Authorship

All authors certified fulfilment of ICMJE authorship criteria.

Author Disclosure

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