

Title: A Tale of Two Patients with Hypersensitivity Reactions to Levothyroxine

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Abbreviations: LT4: Levothyroxine

TRT: Thyroid replacement therapy

IV: Intravenous

ST: Skin testing

ID: Intradermal

DPT: Drug provocation test

IDT: Induction of tolerance

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Abstract

Hypothyroidism is common in the general population, and levothyroxine (LT4) is the treatment of choice. LT4 is well tolerated in the majority of the patients, and allergic reactions are rare, with only a few reported cases of LT4 drug hypersensitivity reactions (DHR)¹⁻³; However, due to the synthetic nature of this drug, it is suggested that hypersensitivity can be induced under certain pathologic conditions, such as autoimmune disorders⁴. We present two cases of DHR to thyroid replacement therapy (TRT) with subsequent management by drug provocation test (DPT) and induction of drug tolerance (IDT).

Case description

Patient 1 is a 45-year-old female diagnosed with papillary thyroid cancer who was started on levothyroxine (LT4) after thyroidectomy. She developed multiple adverse reactions (i.e., nausea, vomiting) to different oral formulations, including generic LT4, Synthroid®, Armour®, and Cytomel®. Despite thyroid replacement therapy (TRT), her TSH was above goal and due to gastrointestinal intolerance, she was switched to intravenous (IV) LT4 infusion. The patient developed flushing, dysphagia, urticaria, and angioedema within 30 minutes of the first dose requiring treatment with IV diphenhydramine and methylprednisolone. She was then evaluated by the allergy department. Skin testing (ST) was negative [Levothyroxine 50mcg/mL skin prick test 1:10; intradermal (ID) 1:100,000] and was unable to complete higher ID concentrations due to pruritus. The patient declined drug provocation test (DPT). She completed a 13-step oral induction of tolerance (IDT) protocol with only mild lip/nose pruritus during step #10, which was treated with intramuscular diphenhydramine (**Table I**). The patient has tolerated the medication to date without further reactions.

Patient 2 is a 70-year-old woman with multiple self-reported drug allergies and history of Hashimoto’s Thyroiditis who initiated treatment with 25 mcg of oral LT4 daily. Despite treatment, her TSH was persistently out of range (> 5.0 ; 0.3-4.2 mIU/L), and her medication was switched to Synthroid® 50 mcg. The patient developed dysphagia and lip swelling within the first three hours of administration, requiring treatment with IV diphenhydramine and oral prednisone with resolution of symptoms. She discontinued Synthroid® after these episodes and avoided TRT for one year due to fear of further reactions. Due to uncontrolled hypothyroidism as evidenced by an increased TSH (5.9; ref. 0.3-4.2 mIU/L) and a low free T4 (0.8; ref. 0.9-1.7

ng/dL), the patient required re-initiation of TRT. The patient declined ST. The content of each LT4 preparation was reviewed for excipient/fillers. Tirosint™ was found to have the least number of excipients and fillers (levothyroxine sodium, gelatin, glycerin, and water). The patient underwent a two-step DPT with Tirosint™ without adverse reactions and has tolerated the medication to date.

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74 Discussion

Hypersensitivity reactions to hormones are extremely unusual. DHR related to LT4 can be secondary to either the active or inactive components such as fillers or excipients.⁵ Specifically, dyes are an important cause of allergic reactions.^{1, 5} Currently, there are nine FDA-approved LT4 formulations in the United States, including tablets, soft gel, and liquid preparations, with the tablet LT4 being the most widely used preparation.⁶

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The initial approach for suspected LT4 immediate hypersensitivity reaction is to perform ST. However, the reference standard for DHR testing is a DPT, as no validated TRT ST presently exists.⁷ Patient 1 presented with symptoms suggestive of an IgE-mediated reaction (i.e., urticaria, angioedema) and had negative ST. The patient then declined DPT, so though to the high pre-test probability and the lack of valid TRT ST the patient underwent IDT. IDT protocols to LT4 have been previously reported in the literature.^{2, 3} Since the patient reported DHRs to different levothyroxine preparations, we entertained an actual allergy to the active ingredient of TRT. Our second patient declined ST but tolerated a DPT to LT4 with the least amount of non-active ingredients without further adverse reactions.

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To summarize, since TRT allergy is a rare condition and there is no validated ST that can confirm the diagnosis, evaluating patients with suspected DHR to TRT may be challenging. Approaching this type of patients is based on clinical presentation. When there is a high pre-test probability of an IgE-mediated reaction ST or IDT should be considered. Contrarily, if there is a low pre-test probability, DPT is the recommended step. For patients with documented DHR to TRT and no available alternative treatments, IDT is warranted.⁷ Due to the necessity of hormone replacement therapy in patients with hypothyroidism, these cases reinforce the need for a thorough evaluation of any reported allergies to thyroid medications.

Learning point for clinicians

Confirmed drug hypersensitivity reactions (DHR) secondary to thyroid replacement therapy (TRT) are unusual. Active or inactive components such as fillers or excipients may be the culprits behind a potential TRT allergy. Categorizing patients with DHR to TRT based on pre-test probability might aid in selecting the best approach between drug provocation test (DPT) and induction of drug tolerance (IDT).

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Table I. Levothyroxine desensitization protocol.

Step	Time (H:MM)	Dose (mcg)	Cumulative Dose (mcg)
1	9:00	0.0125	0.0125
2	9:15	0.025	0.0375
3	9:30	0.05	0.0875
4	9:45	0.1	0.1875
5	10:00	0.2	0.3875
6	10:15	0.4	0.7875
7	10:30	0.8	1.5875
8	10:45	1.6	3.1875
9	11:00	3.2	6.3875
10	11:15	6.4	12.7875
11	11:30	12.5	25.2875
12	11:45	25	50.2875
13	12:00	75	125.2875

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