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REVIEW

Thyrotoxicosis after massive triiodothyronine (LT3) overdose: a coast-to-coast case series and review

Zhiheng H He MD, PhD[1,2], Yan Li MD[3], Nitin Trivedi MD[3], Sabrina Gill MD[4], James V Hennessey MD[2]

[1]Division of Endocrinology, Diabetes, & Metabolism, Department of Medicine, Cambridge Health Alliance, Cambridge, MA, USA; [2]Division of Endocrinology, Diabetes, & Metabolism, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; [3]Department of Medicine, St. Vincent Hospital, Worcester, MA, USA; [4]Division of Endocrinology & Metabolism, Department of Medicine, St. Paul's Hospital, University of British Columbia, Vancouver, BC, Canada

Abstract

Excessive exogenous thyroid hormone ingestion may lead to severe thyrotoxicosis and cause potential harm. We have reviewed the literature and suggested that thyroid hormone supplementation should not be used to alleviate nonspecific complaints in patients with normal endogenous thyroid function. Failure to do so may cause serious harm, as demonstrated in one of the cases described here. In addition, treatment based on symptom relief only without biochemical measure may lead to overmedication – as reported from academic hospitals both in Canada and the United States. Given the risk of severe thyrotoxicosis from potential compounding errors, pharmacies providing a compounding service should be subject to more rigorous monitoring by the food and drug administration. Clinicians should also use local biochemical markers when titrating thyroid hormone supplements even though the normal thyroid function reference range has its limitation, failure to do so may result in iatrogenic thyrotoxicosis.

Keywords: compounding, hyperthyroidism, hypothyroidism, LT3, iatrogenic, thyrotoxicosis, triiodothyronine.

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Introduction

American Thyroid Association guidelines suggest that thyroid hormones should not be used to treat the symptoms suggestive of hypothyroidism without biochemical confirmation[1,2]; however, some clinicians doubt the correct utility of thyroid function testing and some subjects may take over-the-counter supplements with high iodine content or even unlisted thyroid hormones to alleviate their symptoms.[3–5] Excessive iodine intake may lead to hyperthyroidism in patients with chronic iodine deficiency through the Jod-Basedow effect.[6] Furthermore, some patients with hypothyroidism continue to have 'symptoms of hypothyroidism' despite normalization of serum thyrotropin and free thyroxine levels following levothyroxine treatment.[7–9] Patients with persistent symptoms, despite achieving the biochemical euthyroid state following levothyroxine replacement, are sometimes treated with natural thyroid extracts or compounded thyroid hormone preparations. Some providers may even initiate therapy with the combination of LT4 and LT3 as the first-line therapy, even though that is not consistent with the recommendation from guidelines. Iatrogenic thyrotoxicosis may develop from these alternative approaches.

We report three cases of severe thyrotoxicosis induced by the ingestion of compounded thyroid hormone(s). Case 1 was in 2011, Case 2 in 2013, and Case 3 in 2014. These cases were collected independently by three groups of the authors. At the time these patients were seen, none of the institutions involved required specific informed consent from patients as long as patient confidentiality was maintained through anonymity. When this case series was drafted, all institutional requirements had been met. The identities of two of the compounding pharmacies were not known to the authors.

Case 1

A 20-year-old male presented to his primary care physician in Boston, USA with several weeks' history of fatigue and

Table 1. Time course of thyroid function tests (TSH, total T4 and total T3) in the patient described in case 1 over 18 months. Baseline thyroiud function was also listed.

	Baseline	Presentation	Day3	Day 7	6 Months	10 Months	18 Months
TSH (0.27–4.2 μIU/mL)	1.64	0.065	0.047	0.01	4.96	2.76	0.31
Total T4 (4.6–12 μg/dL)	6.6		7.1				
Total T3 (80–200 ng/dL)	117	14982.6	8914.4	1213.8	127	88	

generalized malaise. Although extensive workup was undertaken, including thyroid function tests (baseline lab in Table 1) were unremarkable, he was offered thyroid hormone for symptomatic relief. He was prescribed compounded LT3 10 μg twice a day. Shortly after the ingestion of the second dose, he experienced severe anxiety, palpitations, agitation, and shortness of breath and presented to a local emergency department (ED). En route to the ED, he was informed by the compounding pharmacy that the capsule might contain an excessive amount of LT3 due to a compounding error.

In the ED, the physical exam was significant for irritability, tachycardia, and fine tremor. The thyroid gland was not enlarged to palpation. An EKG showed sinus tachycardia without evidence of ischemic changes. His initial TSH was mildly suppressed. He was given a β-blocker for symptomatic relief and discharged home. He was instructed not to continue with the compounded medication. However, the patient continued to experience thyrotoxic symptoms that prompted multiple ED visits in the following weeks. Multiple thyroid function tests were performed during these visits that showed dynamic changes (Table 1). Interestingly, EKG and echocardiogram showed regional ischemic changes, consistent with elevations of troponin, creatine kinase (CK), and CK MB isozyme, which returned to normal 8 months later. At this time, one of the remaining LT3 capsules was sent out to an independent laboratory for analysis, which revealed that it contained 10,794.4 μg of LT3, more than 1000-fold higher than intended. His thyroid function was normal 8 months after the incident without thyroid hormone treatment, and no further intervention was indicated.

Case 2

A 30-year-old woman in Vancouver, Canada was diagnosed with subclinical hypothyroidism and was treated with levothyroxine. She was subsequently prescribed desiccated thyroid and later switched to triiodothyronine (Cytomel^{R}) 25 μg daily with eventual improvement in her energy level. Two years later, she was seen by a naturopath who switched her to a compounded LT3 controlled release 15 μg twice per day preparation with normal thyroid function 2 months before the presentation of her symptoms.

She presented to the ED with a 3-day history of nausea, vomiting, abdominal pain, and severe headache. She had negative head imaging and was discharged with improvement on narcotics. Laboratory results were unremarkable although thyroid function was not checked. She was documented to be taking 'thyroid supplements' without elaboration. She continued to take the compounded LT3 unnoticed by her healthcare providers. Two days later, she was brought to ED for confusion, disorientation with persistent nausea, vomiting, diplopia, and headache. She was mildly febrile at 37.7°C and sinus tachycardia of 115/minute. Serum and CSF biochemical studies, toxicology screen, and CT of the head were all negative. She was treated empirically with intravenous ceftriaxone, vancomycin, and aciclovir with a presumptive diagnosis of encephalitis. At this admission, thyroid tests revealed thyrotoxicosis (Table 2), and a diagnosis of thyroid storm was made. All her medications and multiple supplements were obtained from her residence, and it was recognized that she was taking compounded LT3 with a new prescription filled 16 days prior to her admission. She received cholestyramine by nasogastric tube and intravenous glucocorticoids initially, and plasmapheresis with albumin exchange was initiated. One day post dialysis, her FT3 declined by 50%. There was a gradual decline in FT3 levels over the ensuing 10 days and her level of consciousness improved by day 9 post dialysis (Table 2). She was discharged 2 weeks post admission. Her thyroid function remains within the normal range 6 weeks after the discharge without thyroid hormone treatment.

Subsequent analysis of the capsules of compounded triiodothyronine controlled release revealed contents containing 15,000 μg LT3 per capsule (1000 times the intended content). Thus, she had consumed a cumulative dose of 480,000 μg LT3 before her admission.

Case 3

A 44-year-old woman in suburban Boston, USA presented with a 3-day history of headaches, dizziness, palpitations, tremor, mild abdominal pain, and nausea. Approximately 5 years earlier, she had developed primary hypothyroidism and was initially treated with levothyroxine for 2.5 years. Despite achieving normal levels of TSH and free T4, she had persistent fatigue, weight gain, and continually 'felt unwell'. For this reason and patient preference, LT4 was switched to compounded liothyronine/levothyroxine (LT3/LT4) 6 months before admission. She initially experienced modest improvement in her symptoms. Her TSH, total T3, and free T4

Table 2. Time course of thyroid function tests in the patient described in case 2.

	Initial presentation (ON Compounded LT4/LT3)	At discharge	10 days post discharge
TSH (0.27–4.4μU/L)	<0.02		2.56
FT4 (10–22 pmol/L)	11	6	12
FT3 (3.5–6.5 pmol/L)	>30.8 (diluted: 330)	3.6	3.3
TR-Ab (<1.8 IU/L)	<0.9		
TPO-Ab (<36 KIU/L)	11		
Tg (<60 μg/L)	2		
Tg-Ab (<41 KIU/L)	Negative		

Table 3. Dynamic changes of thyroid function over 1 month in the patient described in case 3.

	Presentation (On Compounded LT3/LT4)	1 Week*	2 Weeks	1 Month
TSH (0.27–4.2 μIU/mL)	0.025	0.012	0.015	2.62
FT4 (0.93–1.7 ng/dL)	>7.77	2.89	1.67	1.09
TT3 (71–180 ng/dL)	>651	220	124	90

*Time was counted from the first day of taking the erroneously dosed medication.

were within normal range 2 months before her presentation while on a stable dose of the compounded medication.

Three days before presentation, the patient refilled a new batch of the compounded LT3/LT4 from a specialty compounding pharmacy. On the day of admission, she was notified by her pharmacy that her medication was accidently compounded to ten times the usual amounts of LT3 and LT4. Thus, she came to the emergency room for further evaluation. The initial vital signs revealed a temperature of 96.9°F (36.1°C), blood pressure 123/69 mmHg, and heart rate 75/minute, which was high for the patient, as she was a runner with a baseline heart rate in the 50s. Physical examination was unremarkable except for a diffuse firm goiter, minimal hand tremor, and anxious appearance. Laboratory results are shown in Table 3. The EKG showed sinus rhythm with a heart rate of 70/min. The compounded medication was held and cholestyramine was administered. There was a significant decrease in the levels of thyroid hormone within a few days, as shown in Table 3.

Review of literature and conclusion

We present three patients with thyrotoxicosis induced by compounded thyroid hormones either LT3 alone or combination of LT3 and LT4. Due to compounding errors, the patients received 10–1000-fold of the intended dose from the pharmacy, and all patients developed severe thyrotoxicosis associated with extremely elevated serum T3 levels. Limited information is available regarding iatrogenic thyrotoxicosis from compounded LT3 preparations. Most of the reports are from pediatric populations without long-term consequences.[10–12] Jha and colleagues reported a 62-year-old female without significant past medical history who presented with thyroid storm due to the ingestion of a 'thyroid supplement' that contained erroneous high doses of both LT3 and LT4 that required plasmapheresis (i.e. similar to one of our cases).[5] Although there is no clear evidence to support thyroid hormone use, especially LT3, for symptomatic relief in patients with normal thyroid function,[9] some providers may offer treatment with thyroid hormone(s) under pressure of patient satisfaction.[13] In addition, many patients aggressively seek treatment, influenced by the large amount of unverified information over the internet. Inappropriate use of LT3 or LT3/LT4 supplements continues to cause harm in euthyroid patients.[3,4] At this time, most guidelines recommend biochemical documentation of persistent hypothyroidism before treatment[1,2]; however, more research is needed in this field because the three cases we presented here underline the importance of biochemical surveillance, the ignorance of which may cause serious harm.

It is important to note that all three patients described here obtained LT3 or LT3/LT4 preparations from compounding pharmacies. This industry is not as tightly regulated as pharmaceutical manufacturers. In the United States, the industrial manufacture of pharmaceutical products became common following the 1938 Food, Drug and Cosmetic Act that regulated drug safety and labeling.[14] Further regulations imposed in 1962 (Kefauver-Harris Amendments) required drug manufacturers to prove safety and efficacy of the products provided to the public.[14] However, neither of these regulations specifically apply to compounding pharmacies. More recently, specialized compounding pharmacies have reemerged with the philosophy that individualized dosing and ingredients (as prescribed by a physician) could deliver medications that were tailored for patients specifically. The thousands of compounding pharmacies across the United States are not registered with the FDA, and are neither subject to federal recordkeeping nor reporting rules. The FDA can even be blocked through litigation from visiting the compounders should issues arise.[14] As a result, this practice has not been under effective monitoring for quality, precision, and safety[14,15] and may bring harm to patients due to the lack of supervision.[16] Compounders may alter the composition and excipients to generate the 'extended released' products without extensive pharmacokinetic data. It is sensible that products from compounding pharmacies should be closely monitored by federal or state/provincial agencies, like any other pharmaceutical industry. Compounding errors may occur when good manufacturing practice (GMP) regulation is not mandated.[17] The three cases here provided such supporting evidence to call for action to properly control this industry.

In summary, we have reported three cases of iatrogenic thyrotoxicosis due to compounding pharmacy errors in both the United States and Canada, from the west to the east coast of North America. All cases received nonguideline supported pharmacological intervention based on nonspecific clinical evidence of hypothyroidism. These cases highlight a need for regulation of compounding pharmacies to the same standards as the pharmaceutical industry.

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Correspondence: James V Hennessey, MD, Division of Endocrinology, Diabetes, & Metabolism, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA, 02215, USA. jhenness@bidmc.harvard.edu

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References

1. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid*. 2012;22(12):1200–1235. https://doi.org/10.1089/thy.2012.0205
2. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. *Thyroid*. 2014;24(12):1670–1751. https://doi.org/10.1089/thy.2014.0028

3. Hoang TD, Mai VQ, Clyde PW, et al. Over-the-counter-drug-induced thyroid disorders. *Endocr Pract*. 2013;19(2):268–274. https://doi.org/10.4158/EP12298.OR
4. Daniels GH, Sluss P. Pure T3-thyrotoxicosis from a Mexican weight loss supplement. *Endocr Pract*. 2013;19(3):559–560. https://doi.org/10.4158/EP12388.LT
5. Jha S, Waghdhare S, Reddi R, et al. Thyroid storm due to inappropriate administration of a compounded thyroid hormone preparation successfully treated with plasmapheresis. *Thyroid*. 2012;22(12):1283–1286. https://doi.org/10.1089/thy.2011.0353
6. Chung HR. Iodine and thyroid function. *Ann Pediatr Endocrinol Metab*. 2014;19(1):8–12. https://doi.org/10.6065/apem.2014.19.1.8
7. Saravanan P, Chau WF, Roberts N, et al. Psychological well-being in patients on 'adequate' doses of L-thyroxine: results of a large, controlled community-based questionnaire study. *Clin Endocrinol*. 2002;57(5):577–585. https://doi.org/10.1046/j.1365-2265.2002.01654.x
8. Okosieme O, Gilbert J, Abraham P, et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. *Clin Endocrinol* 2016;84(6):799–808. https://doi.org/10.1111/cen.12824
9. Peterson SJ, Cappola AR, Castro MR, et al. An online survey of hypothyroid patients demonstrates prominent dissatisfaction. *Thyroid*. 2018;28(6):707–721. https://doi.org/10.1089/thy.2017.0681
10. Shilo L, Kovatz S, Hadari R, et al. Massive thyroid hormone overdose: kinetics, clinical manifestations and management. *Isr Med Assoc J*. 2002;4(4):298–299.
11. Ho J, Jackson R, Johnson D. Massive levothyroxine ingestion in a pediatric patient: case report and discussion. *CJEM*. 2011;13(3):165–168. https://doi.org/10.2310/8000.2011.110361
12. Majlesi N, Greller HA, McGuigan MA, et al. Thyroid storm after pediatric levothyroxine ingestion. *Pediatrics*. 2010;126(2):e470–e473. https://doi.org/10.1542/peds.2009-2138
13. Junewicz A, Youngner SJ. Patient-satisfaction surveys on a scale of 0 to 10: improving health care, or leading it astray? *Hastings Cent Rep*. 2015;45(3):43–51. https://doi.org/10.1002/hast.453
14. Outterson K. Regulating compounding pharmacies after NECC. *N Engl J Med*. 2012;367(21):1969–1972. https://doi.org/10.1056/NEJMp1212667
15. Drazen JM, Curfman GD, Baden LR, et al. Compounding errors. *New Engl J Medicine*. 2012;367(25):2436–2437. https://doi.org/10.1056/NEJMe1213569
16. van Oosten BW, Killestein J, Barkhof F, et al. PML in a patient treated with dimethyl fumarate from a compounding pharmacy. *New Engl J Medicine*. 2013;368(17):1658–1659. https://doi.org/10.1056/NEJMc1215357
17. Gudeman J, Jozwiakowski M, Chollet J, et al. Potential risks of pharmacy compounding. *Drugs R D*. 2013;13(1):1–8. https://doi.org/10.1007/s40268-013-0005-9