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CASE REPORT

A rare case of levothyroxine overdose

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Background: Levothyroxine (LT4) can be life-threatening in overdose. There are limited cases reported, most of which are in children. Overdose, though rare, may lead to seizures, arrhythmias, and thyroid storm. Despite its potential for clinical catastrophe, it is underreported, and management guidelines are scarce. Herein, a case of LT4 overdose is reported.
Case: A 36-year-old African male with retroviral disease, mitral valve insufficiency, and Graves' disease post-radioactive iodine therapy, ingested 10 000 µg of LT4 and 500 mg of warfarin in a self-harm attempt. He was stable on arrival, showing no signs of thyrotoxicosis or bleeding. Investigations revealed an FT4 > 100 pmol/l (reference range: 11.9–21.6 pmol/l) and an INR of 10.61. Vitamin K was administered for warfarin toxicity and LT4 was withheld. He was monitored in high care and received psychological therapy.
Discussion: LT4 overdose exceeding 5 000 µg can trigger thyrotoxicosis; however, endogenous compensatory mechanisms, such as increased reverse triiodothyronine (T3) production can delay toxicity. Overdose should be suspected when thyroxine (T4) is markedly elevated with a normal thyroid stimulating hormone (TSH). Management includes beta-blockers and glucocorticoids to inhibit peripheral T4-to-T3 conversion, with cholestyramine administered in severe cases.
Conclusion: This case highlights the critical need for close monitoring, even in the absence of acute symptoms, to prevent late onset fatalities.

Keywords: hypothyroidism, levothyroxine, overdose, thyrotoxicosis, warfarin

Introduction

Thyroid disease has become increasingly commonly diagnosed owing to recent advancements in medical testing and screening. Approximately 200 million people have been diagnosed with thyroid disease globally.[1] Hypothyroidism in particular affects 5–10% of the general population. However, in South Africa, its prevalence is not precisely documented but is estimated to align with global trends.[2]

Levothyroxine (LT4) is a synthetic hormone that is chemically identical to endogenous thyroxine (T4) and is the standard treatment for hypothyroidism.[3] LT4 is absorbed in the small intestine; its rate and absorption are affected by factors such as age and dietary intake. LT4 binds to plasma proteins, but only free T4 (FT4) is biologically active.[4] FT4 is peripherally converted to active triiodothyronine (T3). T3 regulates metabolism, thermogenesis, and protein synthesis, supporting growth, repair, and cellular function. It also influences cardiovascular health, neural development, and energy balance. It is mainly metabolised via deiodination and excreted through urine and faeces after undergoing first-pass metabolism in the liver.[2,4]

The World Health Organization in 2019 reported that one in every eight people suffer from a mental health condition, of whom 20% are likely to use overdose as a mechanism for suicide.[5] There is a paucity of literature outlining cases of LT4 overdose, possibly owing to underreporting, under-recognition, or LT4 being an infrequent choice of drug for overdose. Existing literature reports a few cases of accidental overdose with LT4 among the paediatric population. Some reports have showed that massive LT4 overdose can present with severe manifestations such as thyroid storm, malignant hyperthermia, cardiac arrhythmias, and seizures.[6,7] Herein we present a case of LT4 overdose, and a review of existing literature.

Case description

A 36-year-old African male with a background medical history of human immunodeficiency virus, suppressed on fixed-dose combination antiretroviral therapy containing tenofovir 300 mg, lamivudine 300 mg, and dolutegravir 50 mg daily with no previous opportunistic infections. He has a history of rheumatic heart disease for which he underwent a mitral valve replacement 10 years ago. Postoperatively, he was maintained on anticoagulation therapy to prevent thromboembolic complications (warfarin 5 mg daily), a beta-blocker (carvedilol 25 mg twice daily), and mineralocorticoid receptor antagonist (spironolactone 25 mg daily) to optimise cardiac function. Additionally, he was diagnosed with Graves' disease six years ago for which he had received radio-iodine ablation therapy, and subsequently developed secondary hypothyroidism. He was then placed on LT4 100 µg daily. He presented to the emergency department 11 hours after ingesting approximately 10 000 µg of LT4 (approximately 100 tablets of 100 µg each) and 500 mg of warfarin (approximately 100 tablets of 5 mg each) in a suicide attempt. The precipitants for this index suicide attempt were unemployment and relationship stressors. Upon arrival, he was fully orientated, reported no nausea, vomiting, abdominal pain, syncope, palpitations, or any bleeding. His vitals were stable with a blood pressure of 121/87 mmHg; pulse of 70 bpm, regular; respiratory rate of 18 breaths/minute, temperature of 37 degrees Celsius, SpO2 of 96% on room air, and a blood glucose level of 4.7 mmol/l . Clinically, he had no goitre or features of a thyroid storm, and he was not in

congestive cardiac failure. The rest of his examination was normal. A venous blood gas performed showed no abnormalities. His electrocardiogram showed a normal sinus rhythm with a rate of 76 bpm and his chest radiograph showed a metallic mitral valve but was otherwise unremarkable.

Initial biochemical tests revealed a markedly elevated FT4 level of greater than 100 pmol/l (reference range: 11.9–21.6 pmol/l) (Table 1). The actual level would likely be higher, as the laboratory's upper limit of detection is 100 pmol/l and no dilutions were performed on the sample. The patient had a normal thyroid stimulating hormone (TSH) of 1.52 mIU/l (reference range: 0.27–4.20 mIU/l), suggesting that negative feedback suppression from the hypophysis had not occurred. His international normalised ratio (INR) was also markedly elevated at 10.61 with a prothrombin time of 88.9 seconds (Table 1). The patient was monitored in high care and a dose of Vitamin K was administered for the reversal of warfarin. LT4 and warfarin therapy were withheld; however, his carvedilol and spironolactone were continued. He was monitored for bleeding and his T4 levels and INR were repeated in 48 hours. The psychology department was consulted to assist with mental healthcare.

The patient's FT4 remained elevated at 100 pmol/l until day 7, then decreased to 94.2 pmol/l. The patient remained stable with no signs of thyrotoxicosis or bleeding. By day 11, his FT4 was 46.8 pmol/l and INR 3.08 (Table 1). Anticoagulation was resumed, LT4 was held, and the patient was reviewed by the psychology team, who provided support and coping mechanisms. These included techniques such as cognitive-behavioural therapy for managing negative thoughts, relaxation exercises to reduce anxiety, and breathing techniques to manage stress. The patient was advised to continue these strategies at home and was scheduled for outpatient follow-up with both the psychology and medical teams.

Discussion

We present a case of massive LT4 overdose that followed a benign course with no sympathetic excitation. There are no established guidelines on the management of LT4 overdose given the rarity of reports. Whilst most cases of LT4 overdose exhibit no sympathetic excitation, reports have shown that doses greater than 5 mg are likely to manifest symptoms of thyrotoxicosis such as tachycardia, arrhythmias, palpitations, seizures, diarrhoea, and, in severe cases, a thyroid storm.[8] Although this case followed a seemingly benign course, several important contributing factors warrant consideration. The patient was already on a beta-blocker, which may have masked classic symptoms such as tachycardia and palpitations. However, carvedilol does not inhibit the peripheral conversion of T4 to T3.

Table 1: Biochemical results

Day	TSH (0.27–4.2 mIU/l)	FT4 (11.9–21.6 pmol/l)	INR (2.5–3.5)
0	1.52	> 100.00	10.61
3	1.56	> 100.0	–
7	< 0.01	94.2	8.79
11	–	46.8	3.08

TSH: thyroid stimulating hormone, FT4: thyroxine, INR: international normalised ratio.

Diagnosing LT4 overdose

In patients with hypothyroidism on LT4 therapy who present with suspected drug overdose and have impaired consciousness or are unreliable historians, LT4 should be considered as a potential substance involved in the overdose. Clinically, it is difficult to differentiate whether a patient's raised FT4 levels are secondary to a relapse of a previous hyperthyroid condition or an overdose of LT4. However, a normal TSH and markedly elevated T4 level is suggestive of acute intoxication with LT4, as in the case of our patient and previous reports.[9,10]

Delayed onset of symptoms

LT4 is peripherally converted to biologically active T3 in the tissues and can produce adverse effects when in excess. This process of deiodination occurs during the first 24–48 hours, post-ingestion. Patients can remain asymptomatic during this period and should be closely monitored in a high care setting, however, symptomatic patients can exhibit features of thyrotoxicosis for up to 7 days given the 7.5-day half-life of the hormone.[8,9,11] Patients can remain asymptomatic beyond the first 48 hours, which can be attributed to endogenous biological compensatory mechanisms. These include increased conversion of T4 to biologically inactive reverse triiodothyronine (rT3), which reduces toxicity by competitively binding to thyroid receptors.[8] Additionally, at higher T4 levels, the affinity of T4 to thyroid-binding globulin (TBG) increases, reducing the levels of biologically active thyroid hormone. However, TBG has a finite capacity and can become saturated, leaving excess T4 unbound. Lastly, there is increased hepatic metabolism of excess T4.[8,12]

Management of LT4 overdose

There are a few recommended therapies for the treatment of LT4 overdose. Propranolol, a non-selective beta-adrenoceptor blocker, is preferred as it inhibits the peripheral conversion of FT4 to FT3. At high doses (> 160 mg/day), propranolol has been shown to decrease serum T4 levels.[11] In severe symptomatic cases of LT4 overdose exceeding 10 mg, cholestyramine and glucocorticoids can be considered. Cholestyramine, an ion exchange resin, binds to thyroxine and increases its elimination; it is, however, hepatotoxic and liver enzymes should be closely monitored.[13] Allen et al.[10] recommend the use of corticosteroids in patients with an overdose of LT4 (> 10 mg), especially when the initial FT4 level is above the upper limit, or in any patient with associated adrenal insufficiency. Glucocorticoids such as dexamethasone, prednisone, and hydrocortisone can also be used to decrease the peripheral conversion of FT4 to FT3.[10,11,13,14] Lastly, LT4 should be discontinued until FT4 levels have normalised.

Anti-thyroid drugs such as carbimazole are ineffective in treating LT4 overdose due to endogenous thyroid production already being suppressed. Other treatments commonly used in overdose such as activated charcoal have been shown to have little to no benefit in reducing T4 levels or gastric absorption, despite repeated doses.[15–17] There is conflicting evidence surrounding the use of extracorporeal removal methods. Gill et al.[9] reported limited improvement in serum T4 levels post-haemodialysis in a case of LT4 overdose, possibly due to majority of T4 being protein-bound and not dialysable. Plasmapheresis showed varying degrees of success in the removal of serum T4 and can still be considered in severe cases as a salvage measure.[18–20]

Conclusion

This rare case of LT4 overdose in a 36-year-old male with a history of hypothyroidism highlights the potential for a relatively benign clinical course, even following significant ingestion of LT4. Although most patients with LT4 overdose are asymptomatic or have only mild symptoms, severe cases and delayed symptoms have also been reported. This case emphasises the importance of early identification, close monitoring especially within the first 48 hours, and supportive care in LT4 overdose, particularly in patients with hypothyroidism who have easy access to such drugs. Given the lack of clear treatment guidelines and the rarity of severe outcomes in overdose cases, further research is needed to better define management strategies and improve outcomes in such clinical scenarios, especially those that may not follow a benign course.

Ethical approval

Ethics committee approval was obtained from the Human Research Ethics Committee (Medical) at the University of the Witwatersrand, Clearence certificate number: M240459.

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