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Case Report

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Case Reports of Three Hypothyroid Patients Requiring Very High Doses of Levothyroxine

Chukwuma Ekpebegh

Abstract

Majority of hypothyroid patients achieve and maintain euthyroidism on doses of levothyroxine in the range of 100 to 200 µg per day. This is a report of three patients with hypothyroidism requiring 300 - 450 µg of levothyroxine daily to be euthyroid. These comprised one case of central and two cases of primary hypothyroidism. Contributory factors to high doses of levothyroxine in the patients include use of efavirenz in one patient, morbid obesity and cimetidine therapy in another patient and sodium valproate treatment in the third patient. High doses of levothyroxine may be required to achieve euthyroidism in patients receiving efavirenz, sodium valproate and cimetidine.

Keywords: Levothyroxine; High doses; Hypothyroidism; Efavirenz; Cimetidine; Sodium valproate; Obesity

Introduction

The typical dose of levothyroxine for the treatment of hypothyroidism ranges from 100 to 200 µg per day with estimated requirement of 1.7 µg per kg per day [1, 2]. There are, however, a variety of reasons why higher than expected doses of levothyroxine may be required to achieve and maintain euthyroidism in the hypothyroid [3-6]. These include pseudo absorption [3], drug interference [4], mal-absorption [5] and increased hepatic metabolism of levothyroxine [6]. We report on three of our patients who required much-higher-than-expected doses of levothyroxine to achieve and sustain euthyroid status.

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Endocrinology Clinic, Department of Medicine, Nelson Mandela Academic Hospital Mthatha/Faculty of Health Sciences, Walter Sisulu University, PMB X1, Mthatha 5117, Eastern Cape Province, South Africa. Email: chuksekpebegh@yahoo.com

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Case Reports

Description of three hypothyroid patients managed at the Endocrine Clinic of Nelson Mandela Academic Hospital from 2008 to now requiring much higher than the usual doses of levothyroxine was used to manage other hypothyroid patients. The likely reasons for the higher-than-expected doses of levothyroxine medication are also discussed. Written permission was obtained from the patients to report the cases.

Case 1

A 38-year-old female with Cushings' disease diagnosed in 1998 was initially treated surgically in 1998 and 2004 with a subsequent course of conventional radiotherapy in 2004. She developed panhypopituitarism. Her other co-morbidities include systemic hypertension since 1998, human immunodeficiency virus (HIV) positive on anti-retrovirals therapy since 2008 and bilateral necrosis of both femoral heads with a left hip replacement in 2012. She weighed 78 kg with a height of 1.59 m and a body mass index (BMI) of 30.9 kg/m^2. Her blood pressure was 132/67 mm Hg. Recent results showed normal thyroid hormone levels (serum free T4 of 20 pmol/L and free T3 of 5.4 pmol/L) and CD4 cell count of 580 cells/mm^3.

She maintained biochemical euthyroid profile on a daily levothyroxine dose of 450 µg. Her other medications included daily doses of desmopressin 0.15 mg, hydrocortisone 20 mg, calcium gluconate 3 g, premarin 0.625 mg, medroxyprogesterone 10 mg, enalapril 20 mg, hydrocholorothiazide 12.5 mg, amylodipine 5 mg, atenolol 100 mg, cotrimoxazole two tablets, tramadol 300 mg, diclofenac 150 mg, stavudine 40 mg, lamuvidine 300 mg and efavirenz 600 mg.

Case 2

A 42-year-old female with primary hypothyroidism was diagnosed in 2010. There is also the background history of hypertension, bronchial asthma and peptic ulcer disease. She weighed 134 kg with a height of 1.62 m and a BMI of 51.1 kg/m^2. She was clinically and biochemically euthyroid (se-

rum free T4 of 20.3 pmol/L, serum T3 of 6.6 pmol/L and serum TSH of 0.63 mIU/L) on daily levothyroxine dose of 300 µg. Her other medications included daily doses of frusemide 40 mg, cimetidine 800 mg, simvastatin 20 mg and budesonide 800 µg.

Case 3

An 18-year-old male had congenital primary hypothyroidism, epilepsy and mental retardation. He weighed 58 kg with a height of 1.46 m and BMI of 27.2 kg/m^2. He has remained euthyroid (serum T4 of 15 pmol/L and serum TSH of 1.9 mIU/L) on daily levothyroxine dose of 400 µg. His other medications include daily doses of sodium valproate 800 mg and folic acid 5 mg. Table 1 shows key demographic, diagnoses and treatment profiles for the three patients.

Discussion

These three cases are of patients with frank hypothyroidism on doses of levothyroxine exceeding expected daily doses based on 1.7 µg per kg [2]. The three patients were on stable doses of levothyroxine and their concomitant medications for over 6 months. Patient in case 1 with central hypothyroidism was rendered euthyroid using a dose of levothyroxine that was about thrice the expected dose based on her body weight. She was on several medications including anti-retrovirals which have been shown to reduce serum thyroxine levels in patients on levothyroxine [1]. Thyroid hormone reduction is more commonly reported with protease inhibitors and the suggested mechanism is increased hepatic induction of glucuronyl transferase enzyme with accelerated metabolism of thyroid hormones [1]. Our patient was, however, not on a protease inhibitor-based regimen. We speculate that the increased requirement for levothyroxine is related to use of efavirenz. In one experimental study [7], efavirenz was shown to significantly lower thyroid hormones levels when compared with control patients who were administered similar doses of levothyroxine without concomitant efavirenz.

Patient in case 2 was on a dose of levothyroxine that was about 30% higher than expected for her weight. Contributory factors to the increased requirement for levothyroxine are morbid obesity and use of cimetidine. Cimetidine is a cause of reduced gastric acid acidity, and reduced gastric acid secretion has been shown to impair the absorption of levothyroxine [8]. While cimetidine is regarded as an inhibitor of the hepatic P450 cytochrome oxidase system, in one study [9], it was associated with reduced circulating levels of levothyroxine.

Although hydantoin and carbamazepine anti-coagulants have been shown to result in hepatic enzyme induction [10], there have been inconsistent reports with regard to sodium valproate. While one study [11] showed sodium valproate

Table 1. Demographic Profiles, Diagnoses and Treatments in the Three Cases

Case	Gender	Age	BMI	Type of hypothyroidism	Co-morbidities	Dosage of levothyroxine	Cause(s) of increased levothyroxine requirement
1	Female	38 years	30.9 kg/m^2	Central	HIV positive Hypoadrenalism DI Hypertension AVN both femoral heads	450 µg daily	Efavirenz 600 mg daily
2	Female	42 years	51.1 kg/m^2	Primary	Morbid obesity PUD Hypertension Bronchial asthma	300 µg daily	Morbid obesity and cimetidine 400 mg twice daily
3	Male	18 years	27.2 kg/m^2	Primary	Epilepsy Mental retardation	400 µg daily	Sodium valproate 400 mg twice daily

BMI: body mass index; HIV: human immunodeficiency virus; DI: diabetes insipidus; AVN: avascular necrosis.

to be an enzyme inducer, another [12] found that it had no enzyme induction effects. Our case 3 patient is likely to have required very high doses of levothyroxine as a result of the sodium valproate medication.

These three patients underscore the need to titrate doses of levothyroxine to achieve and maintain clinical and biochemical euthyroidism even where high doses of levothyroxine are required. In case 1 with panhypopituitarism, titration of levothyroxine was made based on the clinical features of thyroid dysfunction and levels of serum free T4 and T3, while in cases 2 and 3 with primary hypothyroidism, clinical parameters and serum TSH level were the primary indices of thyroid status. We continued with the prescriptions of cimetidine and sodium valproate as they were indicated for the treatment of peptic ulcer disease and epilepsy respectively with increased doses of levothyroxine required to maintain euthyroid status. Poor compliance with levothyroxine is an unlikely factor in these patients, as they maintained stable normal levels of free T4, freeT3 and TSH over the last 6-month period.

We have already alluded to increased hepatic enzyme induction notably by anti-convulsants which may lead to increased metabolism of thyroid medication and thus a lower-than-expected serum thyroid hormone response. There are, however, other reasons for increased requirement for levothyroxine. These include conditions that reduce gastric acid secretion such as atrophic gastritis, proton pump inhibitors and antacids [13]. Thyroxine may be bound in the gastrointestinal tract by substances such as ferrous sulphate, calcium salts and cholestyramine [14]. Small bowel disease like coeliac disease may lead to reduced absorption of thyroid hormones [15].

Conclusion

These cases illustrate that a few patients with hypothyroidism will require very high doses of levothyroxine to be euthyroid. While the doses of levothyroxine in hypothyroidism should be titrated to achieve euthyroidism, an understanding of why these high doses are required is necessary. In our patients, concomitant medications, namely efavirenz, cimetidine, sodium valproate were the likely principal factors for the increased doses of levothyroxine.

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