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Case report: Clues to the diagnosis of an unsuspected massive
levothyroxine overdose

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Abstract

There is currently little literature pertaining to levothyroxine overdose apart from minor or accidental overdoses in the paediatric population. In particular there is little information available on how to confidently differentiate levothyroxine overdose from endogenous causes of thyrotoxicosis when there is no history available at the time of assessment.

We report a levothyroxine (15 800mcg) and citalopram (2460mg) overdose in a 55-year-old woman presenting with seizure and tachycardia in which the diagnosis was not initially suspected. Clinical data including a long history of treated hypothyroidism and lack of a goitre; biochemical findings such as an incompletely suppressed thyroid-stimulating hormone (TSH) level despite a markedly elevated free thyroxine level (FT₄), a normal sex hormone-binding globulin level at baseline and an undetectable thyroglobulin supported the diagnosis of thyrotoxicosis due to massive exogenous thyroid hormone overdose. Treatment was given to decrease free triiodothyronine (FT₃) conversion and increase thyroid hormone clearance with dexamethasone and cholestyramine. The patient made a full recovery.

Levothyroxine overdose can result in subtle symptoms and signs clinically, even when in massive quantities. This can make diagnosis challenging. Biochemical features such as the pattern of thyroid hormone elevation and thyroglobulin levels help differentiate exogenous thyroid hormone overdose from endogenous causes of thyrotoxicosis.

Introduction

Levothyroxine is a commonly used medication for hypothyroidism. Despite the large numbers of patients on levothyroxine there is a surprising paucity of cases of overdose reported in the literature suggesting infrequent overdose with this medication, low toxicity, under-reporting, under-recognition of levothyroxine overdose or a combination of one or more of these factors.

Chronic thyrotoxicosis is associated with significant morbidity and premature mortality [1]. A patient that takes an overdose of levothyroxine may be relatively asymptomatic [2] or may develop the following symptoms: hyperthermia [3], cardiac arrhythmias, seizures [4], thyroid storm [5] and even death [3,6]. In the 2012 report from the American Association of Poisons Control Center, levothyroxine was one of the drugs ingested in 9 fatal overdoses [7]. All of these fatal overdoses occurred in adults as part of a polydrug overdose [7]. Outside of the US Poisons center data most published cases are in the pediatric literature and relate to accidental overdose [2, 4, 5, 8-11]. Adult cases have been reported only rarely and may be accidental e.g. due to ingestion of veterinary tablets [12]. In the small group of cases reported the diagnosis is typically evident at presentation i.e. the patient arrives at the hospital already known to have taken an overdose [13-16]. When there is no information at presentation to support an overdose, diagnostic confusion can occur. This may result in a missed opportunity to identify and initiate treatment for a polydrug overdose and/or result in the administration of unhelpful and potentially harmful therapies if, for example, specific therapy for Graves' disease is initiated.

The aims of this case were to describe the biochemical findings diagnostic of exogenous thyroid hormone overdose as compared to endogenous causes of thyrotoxicosis and briefly summarise the management of levothyroxine overdose and where it differs to that of Graves' disease.

Case description

A 55-year-old woman presented to the emergency department (ED) with confusion, dizziness and vomiting. Shortly after arrival the patient had a tonic-clonic seizure lasting less than one minute. Due to the reduced level of consciousness no history was available from the patient but the medication brought in with her by the ambulance staff included levothyroxine and citalopram. From the hospital chart it was noted that the patient had a past history of Graves' disease treated with radioactive iodine in 1993 and had been receiving levothyroxine (900mcg per week). Thyroid function tests were normal 10 months earlier. Family members present at the initial assessment denied that she would ever consider overdose and no corroborating history was available from the patient. There was no history of recent weight loss or thyrotoxic symptoms noted by the family members.

On examination she was afebrile and normotensive with a pulse of 100 beats per minute. Neurologic exam revealed a Glasgow coma score (GCS) of 9/15, pupils were equal and reactive to light but nystagmus was present in all directions. She was hyper-reflexive and ankle clonus was present. She had no meningism. There was no goitre or thyroid bruit.

Complete blood count, urea and electrolytes, calcium and glucose were unremarkable. A CT brain was normal. Thyroid function tests were markedly abnormal (Table 1) with a FT₄ level elevated above the upper limit of quantification of the assay, high FT₃ and incomplete TSH suppression.

The initial working diagnosis was a suspected thyroid storm due to recurrent Graves' disease and she was referred to the endocrine team.

Given the biochemical severity of thyrotoxicosis despite an incompletely suppressed TSH, long duration of hypothyroidism, lack of recent symptoms and absence of a goitre, a polydrug (including levothyroxine) overdose was suspected. An urgent sex hormone binding globulin (SHBG) level was within the reference range (Table 1) and thyroglobulin was undetectable confirming the clinical suspicion of excess exogenous thyroid hormone ingestion. Treatment was commenced with dexamethasone 8mg daily and cholestyramine 1g QID. Cardiac monitoring was performed. Beta-blockade was not given due to a history of asthma.

The patient's GCS normalised within the next four hours, she remained haemodynamically stable with no dysrhythmias. When alert she admitted an intentional overdose of levothyroxine (15 800mcg), and citalopram (2460mg) approximately 18 hours prior to presentation due to recent severe social stressors.

Cholestyramine was continued until FT₄ levels were <50pmol/L with regular monitoring of thyroid tests until the free thyroid hormone levels normalised. TSH

receptor antibodies (TRAb) were positive at 4.4U/L (normal <1.3U/L). Following psychiatric assessment she was discharged well on day 5.

Discussion

We describe a case of massive levothyroxine overdose associated with co-ingestion of citalopram. Both citalopram and levothyroxine may have resulted in hyperreflexia and clonus. The citalopram was most likely responsible for the presentation with a seizure as this agent is known to increase seizure risk particularly in doses >600mg [17].

Attributing the seizure to her thyroid dysfunction potentially risked missing the diagnosis of overdose. It is important to diagnose an overdose as specific therapy may be required in addition to the need for psychiatric assessment.

Thyroid endocrinology

Common symptoms and signs of thyrotoxicosis include weight loss, palpitations, nervousness, tremor, tachycardia, goitre, sweating, and thyroid eye signs [18].

However, elderly patients may present with minimal symptoms (apathetic thyrotoxicosis) [18]. The typical laboratory findings in thyrotoxicosis are of elevated FT₄ and FT₃ levels with a suppressed TSH due to the negative feedback of free thyroid hormones on the pituitary. This is true for any cause of thyrotoxicosis including that of excess exogenous thyroid hormone administration with only rare exceptions e.g. secondary hyperthyroidism from a TSH-secreting pituitary tumour. T₃ is the active hormone and in addition to its secretion from the thyroid, is also

produced from peripheral conversion of T₄. Levothyroxine is a synthetic preparation of T₄ which is also converted to T₃ within the body. Patients receiving adequate levothyroxine replacement should have normal levels of FT₄, FT₃ and TSH. Levothyroxine (T₄) overdose may result in delayed symptoms for several days after overdose as FT₄ needs to be converted to the active FT₃ [19].

Diagnosis of levothyroxine overdose

At initial presentation this patient had extremely high FT₄ levels with an incompletely suppressed TSH level. While this patient may have had endogenous thyrotoxicosis such as due to a late relapse of her Graves' disease there are a number of factors pointing towards the cause being due to exogenous thyroid hormone. The most common causes of thyrotoxicosis are Graves' disease, toxic multi-nodular goitre (TMNG), thyroiditis, and excess levothyroxine replacement (acute or chronic). There are key biochemical findings, which can help emergency physicians differentiate between the various diagnoses of thyrotoxicosis, in particular levothyroxine overdose. Overdose is particularly important to recognise as this may be part of a polydrug overdose requiring specific treatment.

The clinical factors suggestive of exogenous thyroxine being the source of the thyrotoxicosis in this case included the long history of thyroxine use for previously treated Graves' disease, the lack of thyrotoxic symptoms or signs noted by the family members and the lack of a goitre.

Biochemically the pattern of initial thyroid function tests suggested that an acute levothyroxine overdose was likely. In particular, despite the very high FT₄ value (above the upper limit of the assay) the TSH was incompletely suppressed. The

incomplete TSH suppression suggested that the overdose of levothyroxine was likely recent rather than chronic overingestion. This was supported by the normal SHBG level which only peaked at day seven following admission (Table 1). An urgent thyroglobulin was also performed at admission and was undetectable. Thyroglobulin is a protein specific to thyroid tissue, which can be measured from a peripheral blood sample. An undetectable thyroglobulin (in the absence of interfering anti-thyroglobulin antibodies) is confirmation that the cause is not due to endogenous thyrotoxicosis. Thyroglobulin levels will also be undetectable in surreptitious chronic thyroid hormone ingestion (thyrotoxicosis factitia). TRAb are not useful to help differentiate recurrent Graves' from levothyroxine overdose as these may be elevated for many years following radioactive iodine therapy [20] as demonstrated in this case.

This patient was initially referred to an endocrinology consultant service as having a presumptive thyroid storm. A scoring system, developed by Burch and Wartofsky, based on abnormalities in the thermoregulatory, central nervous, gastrointestinal and cardiovascular systems can be used to help determine whether a patient is likely to have a thyroid storm (Table 2) [21]. Thyroid storm is a rare but important condition associated with a high mortality and requires urgent, aggressive therapy [21]. This patient did not meet the criteria for the diagnosis due to the absence of fever, significant tachycardia or other organ involvement. The only potential supporting feature other than thyrotoxicosis was the seizure (likely citalopram-related) and reduced GCS when postictal.

Thyroxine overdose management

Treatment of levothyroxine overdose should be considered as the following:

1. Decontamination
2. Symptomatic for life-threatening/hemodynamic complications or sympathetic overload
3. Blockade of peripheral conversion
4. Monitoring

Decontamination

Criteria are available as to when decontamination and medical treatment following excess thyroxine ingestion are appropriate [19]. Adults who present with acute ingestion >5000mcg should receive activated charcoal [19]. There is a limited role for gastric lavage in this setting except in very early massive overdose (e.g. >10,000 mcg [19]. In this case the patient presented approximately 18 hours after overdose and so decontamination was not performed.

Symptomatic treatment

Symptomatic treatment for sympathetic over-stimulation (tachycardia, systolic hypertension, widened pulse pressure or a high cardiac output) with beta-blockade (or diltiazem if beta-blockade is contraindicated) is recommended [19]. In addition to the cardiac benefits, propranolol also reduces peripheral conversion of FT₄ to the active FT₃, which does not occur with selective beta-blockers. Given the history of asthma and the haemodynamic stability beta-blockade was not given in this case. Beta-blockade can be started at any time point after presentation and the dose tailored to the clinical situation. Hyperthermia should be treated with acetaminophen and cooling cares [19]. Aspirin should be avoided due to the theoretical risk of increasing free thyroid hormone levels due to displacement from the thyroid hormone binding

proteins [19]. Use of benzodiazepines can be considered if the patient is severely agitated [19].

Blockade of peripheral conversion and increasing thyroid hormone clearance

Dexamethasone can be useful in severe thyrotoxicosis [22] as it reduces peripheral

FT₄ to FT₃ conversion. Dexamethasone was given in this case as the amount of levothyroxine taken was initially unknown, the FT₃ was over three times the upper limit of normal and it was thought that the FT₃ level could further increase, with the potential for cardiac instability. We would recommend considering corticosteroids in the setting of massive levothyroxine overdose (>10 000mcg) especially if the initial FT₄ level is above the limit of quantification of the assay or in any patient with associated adrenal insufficiency. Bile acid sequestrants such as cholestyramine reduce enterohepatic recycling of thyroxine and have been demonstrated to lower thyroid hormone levels in thyrotoxicosis [23, 24] including levothyroxine overdose [25]. Use of these agents in thyrotoxicosis is usually well-tolerated and of low toxicity [24] so could be considered in patients who have taken a large overdose, to increase fecal thyroid hormone clearance.

Iopanoic acid and sodium ipodate reduce peripheral conversion of FT₄ to FT₃ [26].

These agents can be useful for the short-term management of endogenous thyrotoxicosis as they also prevent thyroid hormone secretion acutely. Data on their use in acute levothyroxine overdose is limited to two pediatric case reports where they appeared to be successful [8]. Routine use of these agents in levothyroxine overdose

cannot be recommended due to the limited data available but should be considered in the setting of a thyroid storm [27].

Haemoperfusion and plasmapheresis have been reported to be successful in removing levothyroxine from the serum [28]. These methods are not likely to be necessary for most cases of levothyroxine overdose but could be considered in critically ill patients. However data on the use of these therapies is limited and not all groups have reported plasmapheresis to be efficacious in this setting [14, 29].

Monitoring

Depending on the amount ingested medical assessment for at least 3-4 days following overdose should be considered to assess for signs and symptoms of toxicity, with particular attention to cardiovascular or neurologic (decreased GCS) instability. It is known that the peak thyroxine plasma concentration can occur 2-4 days post ingestion (due to the long $t_{1/2}$ of levothyroxine, approximately 7 days and the need for T_4 to be converted to the active FT_3) [19]. For this reason close monitoring of vitals (BP, heart rate, respiratory rate and temperature) are important. Hospital admission may not always be necessary if the patient is stable and psychiatric assessment advises that the patient can be safely discharged, but the amount of levothyroxine ingestion, comorbidities, particularly underlying cardiac disease, and clinical judgement should be used as markers for safe discharge. However, reassessment for admission should be considered if the patient's condition worsens. Information as to the signs and symptoms of thyrotoxicosis should be provided to the patient and their kin on discharge.

Differences in management from endogenous thyrotoxicosis

Anti-thyroid drugs, such as methimazole are usually the mainstay of treatment for Graves' disease or toxic multinodular goitre but carry a small but significant risk of life-threatening side effects such as agranulocytosis and liver dysfunction [30,31]. Anti-thyroid drugs are not effective in reducing thyroid hormone levels in exogenous thyroid hormone ingestion as endogenous thyroid hormone production is already suppressed. While propylthiouracil also reduces peripheral conversion of free thyroxine (T₄) to free triiodothyronine (T₃) there are other therapeutic alternatives for this, as described above. Antithyroid drugs should not be given in the setting of excess exogenous thyroid hormone ingestion. Symptomatic treatment with beta-blockade and consideration of therapies to reduce peripheral conversion and to increase clearance of thyroid hormone are similar for both situations.

Take Home Clinical Messages

Recognition of levothyroxine overdose is critical for appropriate management. The diagnosis of levothyroxine overdose may be suggested by the history and examination findings.

Biochemical features such as the pattern of thyroid hormone elevation, SHBG, and thyroglobulin levels help differentiating exogenous thyroid hormone overdose from endogenous causes of thyrotoxicosis. These tests are readily available from most hospital laboratories.

The ideal management of levothyroxine overdose is patient dependent. Clinical signs and symptoms are the best indicator for level of intervention required. Antithyroid drugs should not be given in the setting of exogenous thyroid hormone ingestion.

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Table 1 Relevant blood results from admission to day 14

Analyte	D0	D1	D3	D4	D5	D7	D10	D12	D14	RR
FT ₄	>100	>100	>100	>100	70	38	22	17	13	12-22nmol/L
FT ₃	20.2	25.5	21.9	18.2	16	7.9	6	4.9	4.3	3.1-6.8nmol/L
TSH	0.21	0.05	<0.02	<0.02	<0.02	<0.03	0.05	<0.03	<0.03	0.27-4.2mU/L
SHBG*	87		110		98	130	120	110	97	18-114nmol/L
Thyroglobulin	<1									

FT₄ = free thyroxine; FT₃ = free triiodothyronine; TSH = thyroid-stimulating

hormone; SHBG = sex hormone-binding globulin; D=day; RR = reference range

*SHBG levels are raised in all forms of thyrotoxicosis and the normal levels at presentation despite very high thyroid hormone levels suggested that the elevation of thyroid hormone was of recent onset.

Table 2 Diagnostic criteria for thyroid storm (modified from 21).

Parameter		Score	
Temperature (°C)	37.2-37.7	5	
	37.8-38.2	10	
	38.3-38.8	15	
	38.9-39.4	20	
	39.4-39.9	25	
	>40	30	
CNS effects	Mild (agitation)	10	
	Moderate (delirium/psychosis)	20	
	Severe (seizure/coma)	30	
Gastrointestinal/hepatic dysfunction	Moderate (diarrhea, nausea, vomiting abdominal pain)	10	
	Severe (unexplained jaundice)	20	
Cardiac dysfunction	<i>Tachycardia</i>	90-109	5
		110-119	10
		120-129	15
		130-139	20
		≥140	25
	<i>Congestive heart failure</i>	Mild (pedal oedema)	5
		Moderate (bibasal rales)	10
		Severe (pulmonary oedema)	15
	<i>Atrial fibrillation</i>	Absent	0
		Present	10
Precipitant history	Negative	0	
	Positive	10	

A score of ≥45 points is highly suggestive of thyroid storm; 25-44 is suggestive of impending storm; <25 points thyroid storm unlikely