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Thyroid Hormone

Updated: April 15, 2019.

OVERVIEW

Introduction

Thyroid hormones used therapeutically include crude thyroid extracts as well as synthetic forms of L-thyroxine (levothyroxine, T4) and L-triiodothyronine (liothyronine, T3). Thyroid hormone plays an essential role in growth and development and regulates multiple metabolic processes that are responsible for functional homeostasis. When given in high doses, thyroid hormone preparations can cause mild serum enzyme elevations. In addition, standard doses of levothyroxine have been linked to rare instances of mild, immunoallergic liver injury.

Background

Levothyroxine (lee" voe thye rox' een) is an orally available form of T4 that is commonly used to treat hypothyroidism and maintain the euthyroid state. Other forms of thyroid hormone include thyroid extract and triiodothyronine (T3) or liothyronine (lye" oh thye' roe neen). Thyroid hormone is essential for normal growth, particularly of the central nervous system. In adults, thyroid hormone maintains normal metabolism in virtually all organ systems. Thyroxine (T4) is released from the thyroid gland, but is converted in the liver and other tissues to the active form, which is triiodothyronine (T3) which engages thyroid hormone receptors in the nucleus of cells, which together bind to DNA, leading to transcription of thyroid responsive genes that have multiple actions in different cells affecting cell metabolism. Thyroid hormone is necessary for normal growth and development, and deficiency of thyroid hormone results in cretinism in children and hypothyroidism and myxedema in adults with a multitude of symptoms, signs and laboratory abnormalities, including fatigue, weight gain, drowsiness, mental torpor and confusion. Hypothyroidism is readily treated with oral forms of thyroid hormone which have been in clinical use for over 50 years, the most commonly used being desiccated thyroid (Armour Thyroid, 1950s), synthetic L-thyroxine or levothyroxine (T4, Synthroid, Levoxyl and others: 2002), and L-triiodothyronine or liothyronine (T3, Cytomel: 1956). Levothyroxine is currently one of the most commonly prescribed medications in the United States, with more than 100 million prescriptions filled yearly. The current indications are for maintenance of the euthyroid state. Levothyroxine is available in tablets at of 25 to 300 mcg for oral administration and as a lyophilized powder for parenteral use. Levothyroxine is typically started at a low daily dose (25 to 50 mcg) and increased based upon clinical effect and serum levels of thyroid stimulating hormone (TSH) and free T4. The usual adult replacement dose is 75 to 125 mcg daily. Side effects are uncommon at correct replacement doses, but high doses can cause symptoms of hyperthyroidism such as fatigue, weight loss, headache, anxiety, tremor, muscle weakness, tachycardia, cardiac arrhythmias, menstrual abnormalities, irritability, emotional labiality, sleep disturbance and changes in personality.

Hepatotoxicity

There is little information on serum aminotransferase levels during thyroxine therapy, but it is a very commonly prescribed medication and, at conventional doses, has not been linked to serum enzyme elevations. High doses of levothyroxine and other thyroid preparations, however, can cause serum enzyme elevations, typically in a hepatocellular or mixed pattern. Indeed, spontaneous hyperthyroidism can be accompanied by serum enzyme elevations and even jaundice. Minor serum enzyme elevations may also accompany hypothyroidism or Hashimoto disease. The liver test abnormalities accompanying hyper- or hypo-thyroidism generally resolve promptly with establishment of the euthyroid state.

High doses of thyroxine and hyperthyroidism also may exacerbate underlying liver disease including drug-induced liver injury, as has been described with acetaminophen and halothane hepatotoxicity. Overdose of thyroxine, however, does not usually cause liver injury. Thyroid hormones also can have multiple drug-drug interactions and other drugs can cause changes in thyroid status, such as hypothyroidism.

Finally, there have been rare reports of immunoallergic hepatitis or hypersensitivity reactions due to levothyroxine which was associated with enzyme elevations and even mild jaundice. The time to onset ranged from 1 to 8 weeks and symptoms typically included fever and fatigue. The enzyme pattern was usually hepatocellular or mixed. Autoantibodies were not detected, but eosinophilia was common. The fever resolved rapidly upon stopping the thyroid preparation, but liver test abnormalities generally required one to two months to fall into the normal range. In at least one case, switching to another form of thyroid hormone was associated with persistence of fever and a worsening of liver tests. In contrast, waiting until recovery from the liver injury and starting triiodothyronine at a low dose with gradual increase to therapeutic levels was generally tolerated without recurrence. Strikingly, the case reports of liver injury due to levothyroxine and thyroid extract were all reported from Asia and Japan, which suggests a racial and possibly genetic predisposition to this idiosyncratic hypersensitivity reaction. Another possibility, however, was that the cases were due to a locally contaminated commercial preparation of levothyroxine.

Likelihood score: C (probable rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of injury accounting for serum enzyme elevations and jaundice during levothyroxine induced liver injury is likely due to hypersensitivity and is possibly genetically determined.

Outcome and Management

Cases of liver injury attributed to levothyroxine and thyroid extract have been mild-to-moderate in severity and self-limited in course, resolving within one to three months of stopping therapy. Rechallenge with levothyroxine has been reported to result in recurrence of fever and hepatic injury, but in several instances patients have later tolerated liothyronine (T3) as a means of treating the hypothyroidism. There have been no reports of acute liver failure, chronic hepatitis or vanishing bile duct syndrome attributed to levothyroxine therapy.

Drug Class: Thyroid Agents

CASE REPORT

Case 1. Immunoallergic hepatitis due to levothyroxine.

[Modified from: Ohmori M, Harada K, Tsuruoka S, Sugimoto K, Kobayashi E, Fujimura A. Levothyroxine-induced liver dysfunction in a primary hypothyroid patient. Endocr J 1999; 46: 579-83. PubMed Citation].

A 13 year old girl was found to have hypothyroidism thought to be due to Hashimoto thyroiditis with serum TSH levels of 770 µU/mL, free T4 <0.1 ng/dL, thyroid peroxidase antibody 7.9 U/mL, and thyroglobulin antibody 11.8 U/mL. Her serum aminotransferase levels were mildly elevated (ALT 41 U/L, AST 35 U/L, Alk P 176 U/L) and an abdominal ultrasound showed mild fatty liver. She was started on oral levothyroxine in a dose of 50 µg daily which was increased to 150 µg daily. Thyroid test results improved, but she developed fever and mild serum enzyme elevations 3 weeks after starting levothyroxine (Table). The fever persisted despite a decrease in the dose of levothyroxine to 50 mcg daily and she developed fatigue and worsening liver test abnormalities, serum ALT rising to 365 U/L and Alk P to 833 U/L (Table). She had no history of liver disease or risk factors for viral hepatitis and was taking no other medications. Levothyroxine was stopped and her fever resolved within a few days and serum aminotransferase levels began to fall. Four weeks later, she was asymptomatic and liver tests were normal. Because thyroid test abnormalities had returned, low doses of triiodothyronine were started (5 µg daily). Liver tests remained normal and the dose was gradually increased to 50 µg daily.

Key Points

Medication:	Levothyroxine (150 µg daily)
Pattern:	Mixed (R=4.7)
Severity:	1+ (enzyme elevations without jaundice)
Latency:	3 weeks
Recovery:	1 month
Other medications:	None mentioned

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
0	0	41	176	0.4	Hypothyroidism
1 week	0	30			TSH 820
1 weeks	50 µg	42			TSH 81
3 weeks	150 µg	41	207		Fever, TSH 1.9
7 weeks	50 µg	365	629	0.5	Levothyroxine stopped
9 weeks	0	61	833		TSH 100
14 weeks	0	28	566		Liothyronine started
17 weeks	0	21	553		TSH 6.7
Normal Values		**<31**	**<285**	**<1.2**	

Comment

Although widely used, levothyroxine has not been mentioned as a cause of drug induced liver injury in large case series. Nevertheless, at least four cases of liver injury attributable to levothyroxine have been reported from Japan. As in the current case, the time to onset was generally within a few weeks of starting, and the presenting symptoms were fever and fatigue. Liver test abnormalities were mild, but transient jaundice occurred in at least two cases (one during rechallenge). Restarting thyroid replacement with triiodothyronine was generally tolerated, but abrupt switching to other forms of thyroid replacement did not always lead to resolution. The cause of the liver injury is unknown, but is likely to be part of a generalized hypersensitivity reaction. The clinical presentation, however, has been characterized as fever and eosinophilia and rarely drug rash.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Levothyroxine – Synthroid®

DRUG CLASS

Thyroid Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

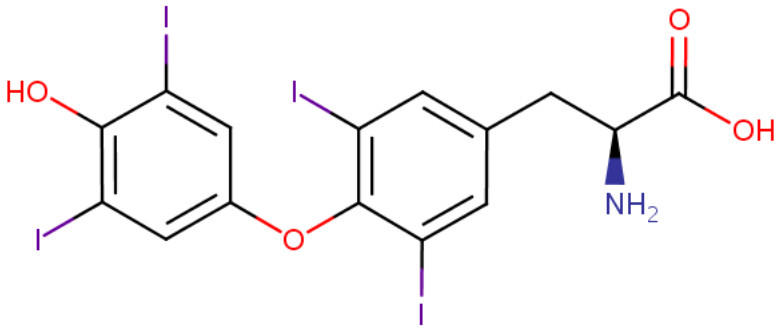
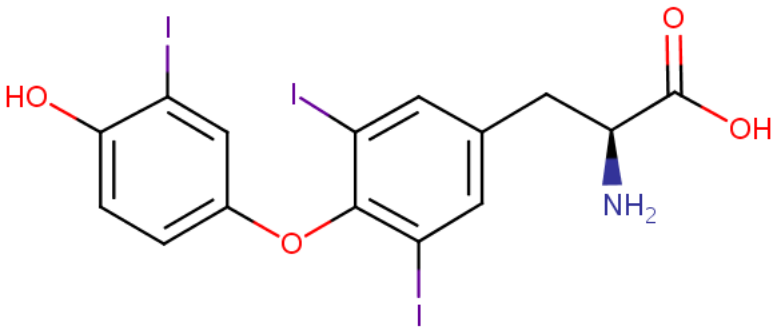
DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Levothyroxine	51-48-9	C15-H11-I4-N-O4	

Table continued from previous page.

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Liothyronine	6893-02-3	C15-H12-I3-N-O4	

ANNOTATED BIBLIOGRAPHY

References updated: 15 April 2019

Zimmerman HJ. Hormonal derivatives and related drugs. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 555-88.

(Review of hepatotoxicity published in 1999; thyroid hormone is mentioned as potentially worsening liver injury due to acetaminophen and halothane, but liver injury due to thyroid hormone alone is not discussed).

Chitturi S, Farrell GC. Adverse effects of hormones and hormone antagonists on the liver. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013: pp 605-620.

(Textbook on hepatotoxicity; antithyroid medications are discussed, but not thyroid hormones).

Brent GA, Koenig RJ. Thyroid and anti-thyroid drugs. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 787-802.

(Textbook of pharmacology and therapeutics).

Inui A, Ishikawa K, Mizuno N, Oimomi M, Baba S. [Case of Hashimoto's disease with thyroxine induced allergic hepatitis]. Nihon Naika Gakkai Zasshi 1983; 72: 1407-13. Japanese. PubMed PMID: 6689558.

(63 year old Japanese woman developed fever and fatigue 2 weeks after starting L-thyroxine [bilirubin normal, ALT 2097 U/L, Alk P ~225 U/L, eosinophilia], resolving rapidly on stopping and recurring with restarting L-thyroxine [bilirubin 6.5 mg/dL, ALT ~1000 U/L, Alk P ~200 U/L with rash and fever], but not after subsequent use of triiodothyronine).

Shibata H, Hayakawa H, Hirukawa M, Tadokoro K, Ogata E. Hypersensitivity caused by synthetic thyroid hormones in a hypothyroid patient with Hashimoto's thyroiditis. Arch Intern Med 1986; 146: 1624-5. PubMed PMID: 3755319.

(63 year old Japanese woman with hypothyroidism developed fatigue 4 months after starting triiodothyronine [T3] [ALT 1044 U/L, bilirubin and Alk P not given], resolving within 1 month of stopping and recurring with fever within 4 days of starting levothyroxine [bilirubin 1.1 mg/dL, ALT 610 U/L, Alk P 717 U/L, 9% eosinophils], fever resolving in 1 day and liver tests in 2 months; she later tolerated slow introduction of triiodothronine).

Mandel SH, Magnusson AR, Burton BT, Swanson JR, LaFranchi SH. Massive levothyroxine ingestion. Conservative management. Clin Pediatr (Phila) 1989; 28: 374-6. PubMed PMID: 2758719.

(29 month old girl ingested 90 levothyroxine tablets [200 µg each] and had high serum T4 levels, but only mild irritability, vomiting and tremor starting around day 4 and resolving within 2 weeks; no mention of ALT elevations or hepatotoxicity).

Mandel SJ, Brent GA, Larsen PR. Levothyroxine therapy in patients with thyroid disease. Ann Intern Med 1993; 119: 492-502. PubMed PMID: 8357116.

(Review of the mechanism of action, clinical efficacy, use and safety of levothyroxine; no mention of hepatotoxicity).

Ohmori M, Harada K, Tsuruoka S, Sugimoto K, Kobayashi E, Fujimura A. Levothyroxine-induced liver dysfunction in a primary hypothyroid patient. Endocr J 1999; 46: 579-83. PubMed PMID: 10580751.

(13 year old Japanese female with hypothyroidism developed fever and malaise within 3 weeks and rising ALT levels within 6 weeks of starting levothyroxine [bilirubin 0.4 mg/dL, ALT 41 rising to 365 U/L, Alk P 207 rising to 853 U/L], fever resolving within days and liver tests within 2 months of stopping, and not recurring with triiodothyronine: Case 1).

Kawakami T, Tanaka A, Negoro S, Morisawa Y, Mikami M, Hojo M, Yamamoto T, et al. Liver injury induced by levothyroxine in a patient with primary hypothyroidism. Intern Med 2007; 46: 1105-8. PubMed PMID: 17634708.

(63 year old Japanese man with hypothyroidism developed liver test abnormalities 2 months after starting levothyroxine [bilirubin 1.5 rising to 11.5 mg/dL, ALT 884 U/L, Alk P 458 U/L], not improving on switching to thyroid extract or triiodothyronine, but resolving when all thyroid was stopped, later tolerating triiodothyronine).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18798340.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, none were attributed to thyroid hormone).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to thyroid hormone).

Warner JV, Morton AP, Hall AJ, Henman MG, Pool LF. Internet slimming, thyrotoxicosis and the liver. Med J Aust 2014; 200: 419-20. PubMed PMID: 24794677.

(34 year old woman developed thyrotoxicosis and mild serum enzyme elevations 8 weeks after starting a Chinese herbal preparation for weight loss [bilirubin not given, ALT 49 U/L, Alk P 121 U/L], improving but with persistence of liver enzyme abnormalities once the herbal preparation [which was shown to contain free thyroxine] was stopped).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to thyroid hormone or levothyroxine).

Kang S, Amino N, Kudo T, Nishihara E, Ito M, Hirokawa M, Miyauchi A, et al. Occurrence of thyroxine tablet (Thyradin S(®)) - induced liver dysfunction in a patient with subclinical hypothyroidism. Endocr J 2015; 62: 719-24. PubMed PMID: 25994001.

(54 year old Japanese woman with hypothyroidism developed liver test abnormalities 5 months after starting levothyroxine [bilirubin 0.4 mg/dL, ALT 233 rising to 369 U/L, Alk P 395 U/L], resolving when switched to a powdered form of thyroid hormone, suggesting a contaminant in the thyroxine tablet).

Li C, Tan J, Zhang G, Meng Z, Wang R, Li W, Zheng W. Risk factors of hyperthyroidism with hepatic function injury: a 4-year retrospective study. Horm Metab Res 2015; 47: 209-13. PubMed PMID: 24867136.

(Among 1070 patients with new onset Graves disease evaluated at a single, Chinese referral center, liver tests were abnormal in 709 [66%], those with abnormalities tending to be older and having more severe hyperthyroidism).

Kim CW, Park JS, Oh SH, Park JH, Shim HI, Yoon JW, Park JS, et al. Drug-induced liver injury caused by iodine-131. Clin Mol Hepatol 2016; 22: 272-5. PubMed PMID: 27209646.

(47 year old woman with thyroid cancer developed a mild episode of hepatitis 10 days after receiving iodine-131 [bilirubin 2.0 mg/dL, ALT 1632 U/L, Alk P 713 U/L, TSH 23.6 mIU/L], responding to corticosteroid therapy and ultimately resolving).

Wang R, Tan J, Zhang G, Zheng W, Li C. Risk factors of hepatic dysfunction in patients with Graves' hyperthyroidism and the efficacy of 131 iodine treatment. Medicine (Baltimore) 2017; 96: e6035. PubMed PMID: 28151911.

(Among 2385 patients with new onset Graves disease, 65% had at least one abnormal liver test [details not provided], which usually improved with successful radioactive iodine therapy [Li 2015]).

Duong N, Lee A, Lewis J. Case of acute mixed liver injury due to hypothyroidism. BMJ Case Rep 2018; 2018: bcr-2017-222373. PubMed PMID: 29367365.

(77 year old woman with hypothyroidism had elevated liver tests [bilirubin 0.4 mg/dL, ALT 264 U/L, Alk P 211 U/L] that improved with levothyroxine replacement therapy [ALT 37 U/L]).