

Received: 2025.03.06
Accepted: 2025.07.06
Available online: 2025.08.26
Published: 2025.09.30

Severe Liver Dysfunction Within 48 Hours of Thionamide Therapy in Thyrotoxicosis: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 **Christopher Annabi**
ABCDEF 2 **Laila Noor**
ABCDEF 2 **Jamie A. Mullally** 

1 School of Medicine, New York Medical College, Valhalla, NY, USA
2 Department of Medicine, Division of Endocrinology and Metabolism, Westchester Medical Center, Valhalla, NY, USA

Corresponding Author: Jamie A. Mullally, e-mail: jamie.mullally@wmchealth.org
Financial support: None declared
Conflict of interest: None declared

Patient: Female, 43-year-old
Final Diagnosis: Drug induced liver injury
Symptoms: Shortness of breath • palpitations
Clinical Procedure: —
Specialty: Cardiology • Endocrinology and Metabolic • Gastroenterology and Hepatology

Objective: Unusual clinical course
Background: Thionamides, including methimazole and propylthiouracil, are medications used to treat hyperthyroidism and have rarely been associated with liver failure. We present a case of fulminant liver failure within 2 days of initiation of high-dose methimazole and propylthiouracil.
Case Report: A middle-aged woman with Graves disease was found to have biochemical hyperthyroidism and SARS-CoV-2 infection. She was started on methimazole, metoprolol, dexamethasone, and remdesivir. On hospital day 2, she developed atrial fibrillation with rapid ventricular response and flash pulmonary edema, requiring intubation. Methimazole was switched to propylthiouracil. On hospital day 3, severe elevations in aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels were noted. Propylthiouracil was held, and liver biopsy demonstrated findings consistent with drug-induced liver injury. Liver function tests gradually improved over the subsequent weeks, with supportive measures. Once stabilized, the patient underwent a successful and uneventful total thyroidectomy and ultimately recovered fully. Most notable in our patient was the rapid onset of fulminant liver failure within 48 h of thionamide initiation, a finding that has yet to be reported elsewhere.
Conclusions: This case demonstrates an earlier timeframe for liver injury from thionamide use than is typically expected. Risk factors may include high-dose methimazole and propylthiouracil exposure as well as concurrent SARS-CoV-2 infection and brief treatment with remdesivir.

Keywords: Chemical and Drug Induced Liver Injury • Endocrine System Diseases • Liver Failure • Methimazole • Propylthiouracil • Thioamides • Thyroid Hormones

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/948822>

 1676  2  2  18



Publisher's note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher

Introduction

Methimazole and propylthiouracil are thionamide medications used to treat hyperthyroidism, with a rare but serious potential for hepatotoxicity. Historical retrospective data include rare cases of acute liver failure from thionamides, with onset most commonly 1 to 3 months after starting a thionamide [1]. The earliest reported cases were 3 to 7 days after initiation of propylthiouracil [2]. To the best of our knowledge, no case has been reported in which acute liver failure developed sooner than 3 days after initiation of a thionamide. Here, we describe a unique case of rapid-onset fulminant liver failure within 48 h of starting high-dose methimazole followed by propylthiouracil.

Case Report

A 43-year-old woman with Graves disease presented to an outside hospital in upstate New York in the fall of 2022 with weakness and upper respiratory symptoms. The patient was alert, oriented, and conversant, and review of systems was notable only for recent unintentional weight loss. The patient reported intermittent use of methimazole for management of her Graves disease. Initial vital signs and physical examination were unremarkable. Laboratory investigations showed normal liver function tests (LFTs), international normalized ratio of 5.2, and positive COVID-19 polymerase chain reaction results. Thyroid laboratory values showed biochemical thyrotoxicosis (Table 1).

Treatment with methimazole was initiated, at a dose of 40 mg every 12 h. She was also started on metoprolol, dexamethasone 6 mg, and given a single dose of remdesivir 100 mg. On hospital day 2, the patient was found to have atrial fibrillation, with rapid ventricular response and flash pulmonary edema, requiring intubation. She was then treated for presumed thyroid storm. Methimazole was stopped and propylthiouracil, at a dose of 200 mg every 4 h, was started. Stress-dose hydrocortisone, an esmolol drip, potassium iodine drops, and cholestyramine were also started. On hospital day 3, severe LFT abnormalities were noted, including aspartate aminotransferase (AST) 6647 (reference range <35 U/L), alanine aminotransferase (ALT) 1694 (reference range <55 U/L), and total bilirubin 8.4 (reference range <1.3 mg/dL). Propylthiouracil was held, and on hospital day 4, she was transferred to our hospital for a higher level of care and evaluation for liver transplantation. Upon arrival, she was intubated and sedated with propofol. Laboratory test results showed an international normalized ratio of 3.3 and significant elevations in LFTs, and thyroid function tests (measured by chemiluminescence immunoassay) showed a low thyroid stimulating hormone (TSH) but normal free thyroxine (FT4) (Table 2).

Table 1. Thyroid function on initial presentation at outside hospital.

	Reference range	Hospital day 1
TSH (mIU/L)	0.350-4.70	<0.002
Free T3 (pg/mL)	2.0-4.4	6.75
Total T4 (mcg/dL)	5.0-12.0	18

TSH – thyroid stimulating hormone; T4 – thyroxine;
T3 – triiodothyronine.

Table 2. Liver and thyroid function on admission to our hospital.

	Reference range	Hospital day 4
ALT (U/L)	<55	2728
AST (U/L)	<35	4930
ALP (U/L)	<150	180
Total bilirubin (mg/dL)	<1.3	15.7
TSH (mIU/L)	0.350-4.70	0.002
Free T4 (ng/dL)	0.7-1.9	1.5
Total T3 (ng/dL)	79-149	29.6

AST – aspartate aminotransferase; ALT – alanine aminotransferase; ALP – alkaline phosphatase; TSH – thyroid stimulating hormone; T4 – thyroxine; T3 – triiodothyronine.

Liver evaluation included negative testing for hepatitis (viral and autoimmune), undetectable acetaminophen and alcohol levels, and an unremarkable abdominal ultrasound. On hospital day 11, transjugular liver biopsy was performed, which showed findings consistent with drug-induced liver injury (DILI), including marked cholestatic hepatitis, perivenular necrosis, and severe bile duct damage, with neutrophilic inflammation.

The LFTs gradually downtrended over the subsequent several weeks, with supportive measures. ALT and AST levels normalized, whereas alkaline phosphatase levels decreased and then stabilized at a level slightly higher than normal over a period of 2 to 3 weeks (Figure 1). FT4 and total triiodothyronine (T3) levels remained stable within the normal range over the first 2.5 weeks at our hospital and then subsequently trended upward (Figure 2). Once her condition was stabilized, the patient underwent a total thyroidectomy about 3 weeks after initial presentation. Her operative course was uneventful, and she ultimately recovered fully.

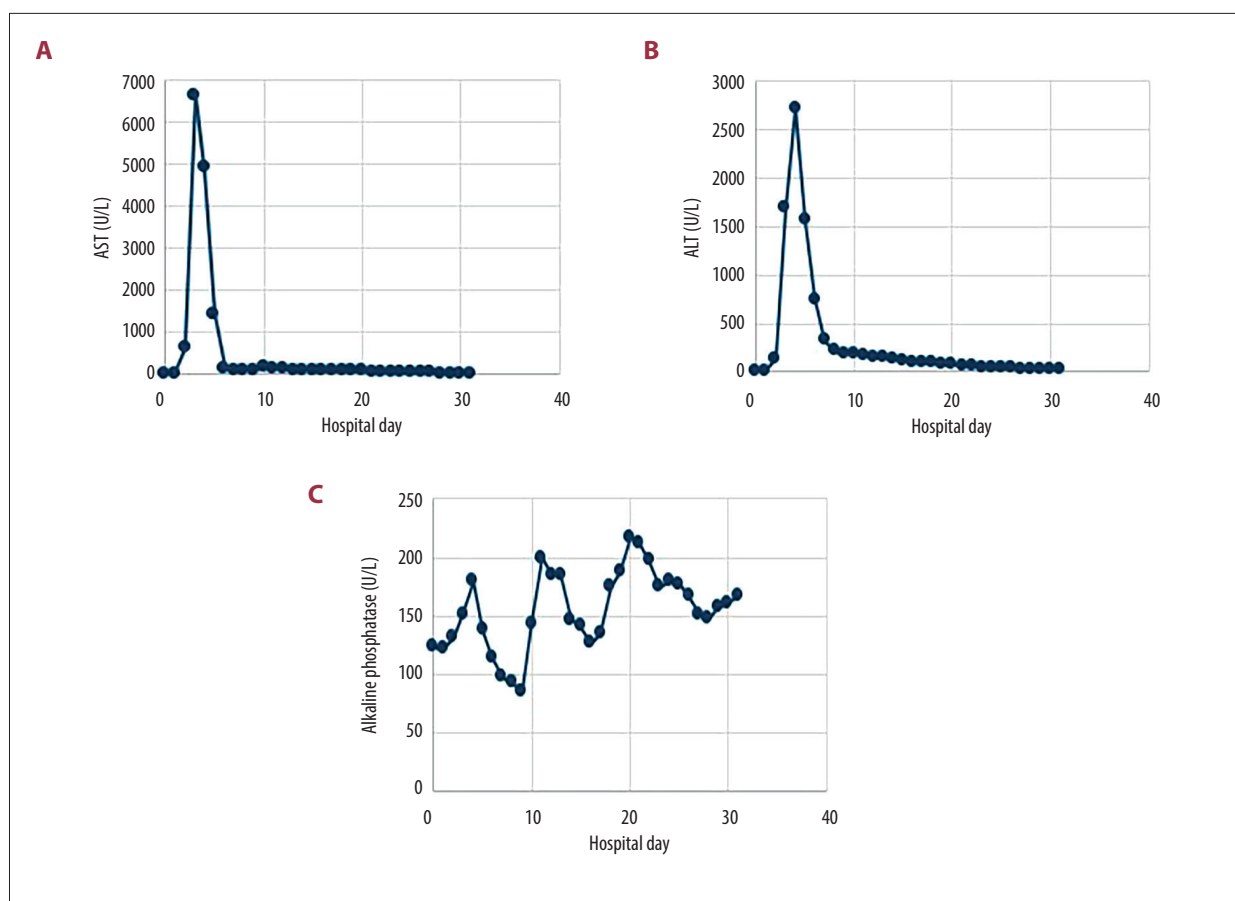


Figure 1. Liver function test results are shown. (A) Aspartate aminotransferase (AST) levels rapidly decreased after cessation of propylthiouracil on hospital day 3 and gradually returned to normal over the following weeks. (B) Alanine aminotransferase (ALT) levels rapidly decreased after cessation of propylthiouracil on hospital day 3 and gradually returned to normal over the following weeks. (C) Alkaline phosphatase levels decreased following cessation of propylthiouracil on hospital day 3 and then stabilized at a level slightly higher than normal in the following 3 weeks.

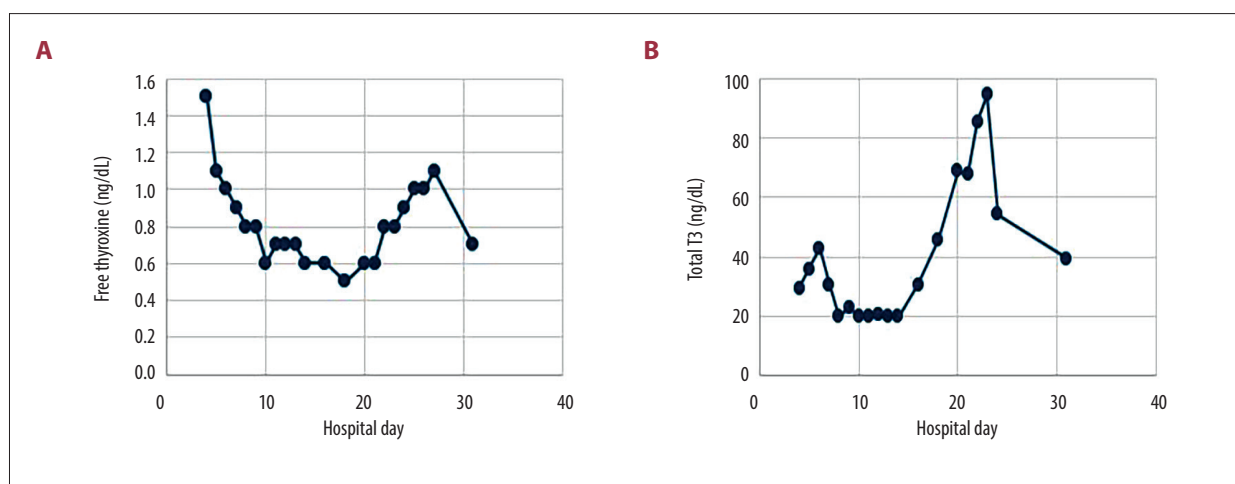


Figure 2. Thyroid hormone levels are shown. (A) Free thyroxine levels steadily decreased within the normal range over the first 2.5 weeks and then subsequently trended upward until a total thyroidectomy on hospital day 23, after which levels decreased. (B) Total T3 (triiodothyronine) levels remained stable over the first 2.5 weeks and then trended upward before total thyroidectomy on hospital day 23, after which levels decreased.

Discussion

DILI accounts for about 10% of all cases of acute liver failure, with an incidence of 1.3 to 19.1 cases per 100 000 [3,4]. DILI is also a rare, albeit major, adverse effect of thionamide therapy.

Thionamides can cause hepatocellular, cholestatic, and mixed hepatocellular and cholestatic patterns of liver injury, which is characterized by hepatocyte necrosis and damage to the biliary system [5,6]. Methimazole was historically thought to cause mainly cholestatic liver injury, while propylthiouracil was thought to mainly cause hepatocellular damage [7-10]. However, more recent studies from Taiwan and China have challenged these observations, suggesting that methimazole was associated with a higher rate of hepatocellular toxicity than propylthiouracil, and that there are similar rates of cholestasis with methimazole and propylthiouracil [1,11,12].

In an analysis of severe DILI from antithyroid drug use in Japan in nearly 19 000 patients newly diagnosed with Graves disease, the prevalence of DILI from methimazole was 1.4%, while propylthiouracil had a DILI prevalence of 6.3%. The prevalence was directly age-related and higher in female patients. Of note, the median time to onset of DILI was 30 days [13].

There is limited case report data describing early-onset liver failure with thionamides. One case describes a middle-aged woman with Graves disease who was treated with methimazole 10 mg 3 times a day and developed liver failure 13 days after methimazole initiation [14]. Another case describes a teenage girl with Graves disease who was treated successfully with propylthiouracil 450 mg daily. Three months later, the patient discontinued propylthiouracil while on vacation, leading to thyrotoxicosis. The patient was restarted on propylthiouracil 450 mg daily but developed liver failure 1 week later [2].

Herein, we report a middle-aged woman with a history of Graves disease who developed significant thyrotoxicosis in the setting of nonadherence with methimazole and acute SARS-CoV-2 infection. Upon treatment with high doses of methimazole followed by propylthiouracil, the patient developed fulminant liver failure within 2 days, with biopsy consistent with DILI. Only when the antithyroid drug therapy was discontinued did the patient's liver function recover gradually over a period of several weeks.

While the previously reported cases demonstrate hepatotoxicity with thionamide therapy, there are important distinctions that make our case unique. In our case, the patient developed liver failure within 48 h of starting thionamides. Prior retrospective studies have demonstrated rare cases of hepatotoxicity from thionamides, with onset most commonly 1 to 3 months after starting a thionamide [1]. The earliest reported cases were 3 to 7 days after initiation of propylthiouracil [2].

Other causes of liver injury can be explored in this patient, such as liver injury from impaired circulation, inflammation from SARS-CoV-2 infection, and remdesivir treatment. While these factors may have contributed to the unusually acute nature of liver injury following thionamide use in this patient, they are unlikely to have been the sole cause of liver injury. Liver injury due to impaired circulation would likely be accompanied by other end-organ damage, such as kidney failure; however, this patient's creatinine level was in the reference range. In addition, liver injury due to impaired circulation would cause extensive centrilobular (zone 3) coagulative necrosis, with relative sparing of the periportal (zone 1) hepatocytes, reflecting the vulnerability of zone 3 hepatocytes to hypoxic conditions. This patient's liver biopsy showed marked cholestatic hepatitis, perivenular necrosis, and severe bile duct damage, with neutrophilic inflammation, all of which are consistent with DILI. Concurrent SARS-CoV-2 infection could have also played a role in the acute nature of this patient's liver injury in the setting of high-dose thionamide use, as SARS-CoV-2 infection alone is unlikely to cause the dramatic increase in transaminase levels seen in this patient. It is also possible that the brief course of remdesivir could have played a role in this patient's liver injury. While a direct pharmacokinetic interaction between methimazole and remdesivir has not been reported, it is possible that remdesivir may have contributed indirectly to the rapid onset of hepatotoxicity in this case, by lowering the threshold for liver injury in the setting of high-dose antithyroid drug exposure. However, we view this as less likely, given that our patient was given only a single dose of remdesivir followed by dexamethasone, which is commonly used after remdesivir to prevent liver injury [15]. In addition, remdesivir is metabolized primarily by CYP3A4, while methimazole is primarily metabolized by CYP2A6 and CYP2A5 enzymes. Furthermore, a systematic review including 22 studies examining drugs causing DILI in the treatment of patients with COVID-19 concluded that the most common adverse effects of remdesivir treatment occurred after 5 to 10 consecutive days of treatment [16]. The review also showed that most cases of liver injury in patients treated with remdesivir consisted of mild to moderate elevation in liver enzymes and did not progress to severe liver injury. Acute liver failure caused by remdesivir was noted in only 2 patients, who had high LFT elevations, as well as coagulopathy and hepatic encephalopathy, with onset between 3 and 10 days of remdesivir administration and rapid resolution upon discontinuation of the drug [17]. Our patient's more prolonged recovery is more consistent with that of methimazole- or propylthiouracil-induced liver injury.

An additional factor that may have contributed to the severity and rapid onset of liver injury in this case is a heightened immune-mediated response to the offending drug. Young and middle-aged women are known to be at increased risk for autoimmune disease, and given that our patient fit this demographic,

it is possible that a vigorous immune response could have contributed to the early development of liver injury. Khan et al reported that approximately 70% of patients with antithyroid drug-related DILI were women, many of whom were of child-bearing age [18]. However, additional studies are needed to better characterize the role of immune-mediated mechanisms in the pathogenesis and timing of antithyroid DILI.

Conclusions

This case demonstrates an earlier timeframe for liver failure from thionamide use than is typically expected and, to the best of our knowledge, represents the earliest onset of hepatotoxicity related to the use of methimazole or propylthiouracil. We hypothesize that the high doses of both the methimazole and propylthiouracil, as well as the patient's intermittent use of methimazole in the past, may have contributed to the very early onset of acute liver failure seen in our patient. However,

data are limited and additional research is needed to clarify the time course and potential risk factors of thionamide-induced hepatotoxicity.

Department and Institution Where Work Was Done

Department of Medicine, Division of Endocrinology and Metabolism, Valhalla, NY, USA.

Patient Consent

The patient provided informed consent for the publication of this case report and its contents.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Yang J, Li LF, Xu Q, et al. Analysis of 90 cases of antithyroid drug-induced severe hepatotoxicity over 13 years in China. *Thyroid*. 2015;25:278-83
2. Williams KV, Nayak S, Becker D, et al. Fifty years of experience with propylthiouracil-associated hepatotoxicity: What have we learned? *J Clin Endocrinol Metab*. 1997;82:1727-33
3. Björnsson ES, Bergmann OM, Björnsson HK, et al. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology*. 2013;144:1419-25
4. Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN prospective study. *Gastroenterology*. 2015;148:1340-52
5. Pauli-Magnus C, Meier PJ. Hepatobiliary transporters and drug-induced cholestasis. *Hepatology*. 2006;44:778-87
6. Holt MP, Ju C. Mechanisms of drug-induced liver injury. *AAPS J*. 2006;8:E48-54
7. Cooper DS, Rivkees SA. Putting propylthiouracil in perspective. *J Clin Endocrinol Metab*. 2009;94:1881-82
8. FDA Drug Safety Communication: New Boxed Warning on severe liver injury with propylthiouracil, April 2010. Available from: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209023.htm>
9. Rivkees SA, Szarfman A. Dissimilar hepatotoxicity profiles of propylthiouracil and methimazole in children. *J Clin Endocrinol Metab*. 2010;95:3260-67
10. Bahn RS, Burch HS, Cooper DS, et al. The Role of Propylthiouracil in the Management of Graves' Disease in Adults: Report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. *Thyroid*. 2009;19:673-74
11. Arab DM, Malatjalian DA, Rittmaster RS. Severe cholestatic jaundice in uncomplicated hyperthyroidism treated with methimazole. *J Clin Endocrinol Metab*. 1995;80:1083-85
12. Wang MT, Lee WJ, Huang TY, et al. Antithyroid drug-related hepatotoxicity in hyperthyroidism patients: A population-based cohort study. *Br J Clin Pharmacol*. 2014;78:619-29
13. Suzuki N, Noh JY, Hiruma M, et al. Analysis of antithyroid drug-induced severe liver injury in 18,558 newly diagnosed patients with Graves' disease in Japan. *Thyroid*. 2019;29:1390-98
14. Gomez-Peralta F, Velasco-Martínez P, Abreu C, et al. Hepatotoxicity in hyperthyroid patient after consecutive methimazole and propylthiouracil therapies. *Endocrinol Diabetes Metab Case Rep*. 2018;2018:17-0173
15. Liu K, Li Z, Li L, et al. mechanistic understanding of dexamethasone-mediated protection against remdesivir-induced hepatotoxicity. *Mol Pharmacol*. 2024;106(1):71-82
16. Sodeifian F, Seyedalhosseini ZS, Kian N, et al. Drug-induced liver injury in COVID-19 patients: A systematic review. *Front Med (Lausanne)*. 2021;8:731436
17. Carothers C, Birrer K, Vo M. Acetylcysteine for the treatment of suspected remdesivir-associated acute liver failure in COVID-19: A case series. *Pharmacotherapy*. 2020;40(11):1166-71
18. Khan AA, Ata F, Aziz A, et al. Clinical characteristics and outcomes of patients with antithyroid drug-related liver injury. *J Endocr Soc*. 2023;8(1):bvad133