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Drug-Induced Liver Injury: A Unique Presentation of Single-Dose Administration of Propylthiouracil

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Abstract

Antithyroid drug-induced severe liver injury is an uncommon but serious complication. We hereby delineate the case of a 38-year-old female who presented to the emergency department for an impending thyroid storm. After initiation of a single dose of propylthiouracil, her liver enzymes went into the thousands. She was subsequently admitted to the intensive care unit. Propylthiouracil was discontinued and corticosteroids were initiated with the resolution of her elevated liver enzymes. On follow-up, her liver function was at its baseline and thyroid hormone levels were under control. We hope this report will encourage clinicians to cast a broad differential diagnosis in patients presenting with liver injury in the acute setting. Furthermore, it is imperative to raise awareness regarding the ever-increasing list of pharmacologic agents that can perpetuate drug-induced hepatotoxicity.

Keywords

drug-induced liver injury, hepatic dysfunction, hepatocellular injury, propylthiouracil

Introduction

Drug-induced liver injury (DILI) is an adverse drug reaction characterized by liver injury. While in certain clinical scenarios DILI may only require discontinuation of the offending agent, intensive care unit admission and even liver transplantation are often resulting phenomena.[1,2] In fact, DILI is the number one cause of acute liver failure in the United States.[1] Although numerous etiologies have been established as culprits of DILI, propylthiouracil (PTU)—an antithyroid medication known to contribute to a mild elevation in liver enzymes—can also lead to hepatotoxicity, a rare phenomenon reported in only 1/10 000 individuals.[3,4] Despite this, it is even more uncommon in a non-obstetric patient (or in those over age 18 years) and/or occurring as an immediate drug reaction, as the onset of injury has typically been observed 2 to 12 weeks after drug initiation.[3-5] In this setting, we present the case of a female with an impending thyroid storm, who developed acute liver injury hours after a single dose of PTU. The aim of this article is to prompt clinicians to cast a broad differential diagnosis in patients presenting with rising liver enzymes in the acute setting, as well as raise awareness as to the ever-increasing list of medications known to perpetuate DILI.

Case Presentation

A 38-year-old female with a history of a multinodular goiter, hyperthyroidism, and iodine allergy presented to the emergency department complaining of palpitations, chest discomfort, and dyspnea. The patient reported that she had recently restarted taking methimazole 10 mg daily after being noncompliant with her medications for the past 3 years. In the emergency department, she was found to be in atrial fibrillation with a rapid ventricular rate and to have an estimated left ventricular ejection fraction of 20%. Laboratory evaluation revealed a suppressed thyroid-stimulating hormone (0.01 mIU/L), elevated free T4 (3.48 ng/dL), elevated free T3 (9.90 pg/mL), and normal liver transaminases. A diagnosis of thyrotoxicosis was made, and treatment with PTU and propranolol was initiated. PTU was chosen due to its inhibition of the peripheral conversion of T4 to T3 and subsequent preference in thyroid storm.

Nine hours after the initial dose of 200 mg PTU, the patient's aspartate aminotransferase and alanine aminotransferase levels showed significant elevation, eventually peaking at 1127 IU/L and 1004 IU/L, respectively (Figure 1). The patient was then transferred to the intensive care unit for close monitoring. Of

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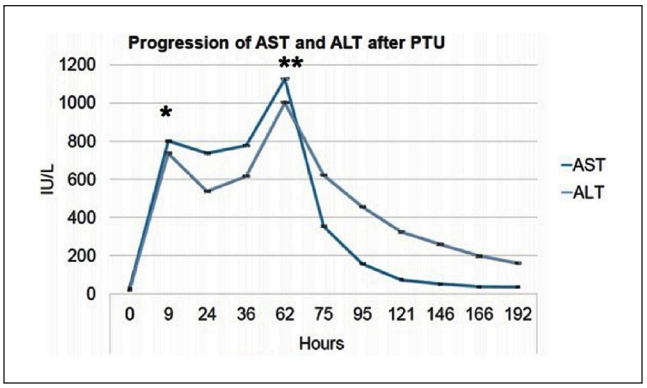

Figure 1. This line graph demonstrates the rapidity in which the liver enzymes increased after a single dose of propylthiouracil (PTU). As shown, hour 0 is when the initial dose of PTU was administered. The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels started to increase immediately after the first dose. At hour 9, as depicted by the single star, PTU was considered the etiology behind acute liver injury and was discontinued after the initial dose. Subsequently, AST and ALT levels peaked at 1127 IU/L and 1004 IU/L, respectively. At hour 62, as depicted by the double star, methylprednisolone was started. It resulted in the eventual normalization of liver enzymes.

note, PTU was not further administered after the first dose due to the evident acute liver injury. This initial treatment was followed by the failure of a tapered regimen of methimazole secondary to persistently worsening liver function.

Intravenous corticosteroids were initiated, resulting in the improvement of both liver and thyroid functions. This allowed for the reintroduction of methimazole without any observed adverse effects. On discharge, the levels of aspartate aminotransferase and alanine aminotransferase were decreased to 38 IU/L and 163 IU/L, respectively. In addition, cardiac function improved with a recalculated left ventricular ejection fraction of 40%. Her hepatitis panels and an autoimmune workup (anti-nuclear antibody, anti-smooth muscle antibody, and anti-mitochondrial antibody) came back as negative. The patient has since had progressive increases in methimazole doses up to 40 mg daily on an outpatient basis. No evidence of further hepatotoxicity was confirmed by a 1-month follow-up, demonstrating complete normalization of liver enzymes.

Discussion

DILI or hepatic dysfunction secondary to pharmacologic therapy presents with elevations in serum levels of liver enzymes in temporal proximity to an offending agent. Numerous pharmacologic agents have been implicated in perpetuating DILI, including herbal supplements, nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, antimicrobial and fungal agents, antiretroviral therapy, lipid-lowering agents, and antidiabetic medications.[1,6-10] While cases of PTU-induced DILI have been described in the biomedical literature, the present case was notable for the rapidity with which liver dysfunction occurred—as after just a single dose of PTU a severe elevation in the transaminases ensued.[11]

Hyperthyroidism and/or her state of hypoperfusion had the potential to cause a rise in liver enzymes. However, liver enzymes of this patient began to normalize while her ejection fraction was still low and amidst an acute episode of thyroid crisis. It is for this reason the authors believe both of those factors did not play a role in the liver injury. Notably, she remained normotensive throughout her clinical course, and liver hypo perfusion, that is, shock liver, can therefore be ruled out as an etiology of her sudden clinically significant hepatic dysfunction. In addition, a hepatitis panel and autoimmune markers were normal, excluding viral hepatitis and/or an autoimmune disease as culprits. Moreover, this patient did not receive acetaminophen or NSAIDs before or during her hospital course, further excluding other known causes of DILI.

The Naranjo scale, an adverse drug reaction assessment score, can be helpful in establishing the degree of association between a drug and an adverse reaction, especially for drug reactions that have not yet been well established or are rarely reported. For our patient, the Naranjo scale score was a 5, rendering DILI a "probable" adverse drug reaction of PTU in this case.[12]

DILI can occur through several pathophysiologic pathways. Most commonly, hepatocellular damage is intrinsic in nature, as it occurs in a predictable dose-dependent fashion, such as seen with acetaminophen toxicity.[13] Conversely, as seen in our case, DILI can occur via an idiosyncratic drug reaction, one that is less predictable and not dose-dependent.[13]

PTU acts by terminating the production of new thyroid hormone via inhibiting the enzyme thyroid peroxidase, which normally facilitates thyroid hormone production. Importantly, PTU also blocks the peripheral conversion of T4 to T3, making it particularly useful in the setting of thyroid storm. As such, it is the recommended agent for thyroid storm and in women during the first trimester of pregnancy.[14]

With regard to the treatment of antithyroid drug–associated acute liver injury, no standard therapeutic strategy is available, except for drug discontinuation and liver function monitoring.[15,16] Notably, anecdotal clinical evidence exists pertaining to the efficacy of intravascular glutathione for methimazole-related hepatotoxicity.[17] Furthermore, Becker and colleagues[18] supported the use of corticosteroids in patients with methimazole-associated transaminitis. Prednisolone may also show a response to alleviate antithyroid drug-induced jaundice.[19] The patient involved in this study showed improvement in both liver and thyroid functions after corticosteroid treatment. Therefore, corticosteroid use may also be evaluated in DILI secondary to PTU. In selected clinical settings, artificial liver support systems or liver transplantation can also be considered in patients with severe DILI secondary to PTU.[11,20]

Conclusions

We highlight PTU as a potential cause of hepatotoxicity after just a single dose. Given the high morbidity and lack of definitive risk factors associated with DILI, this case serves as a stark reminder for clinicians to be mindful and check transaminase levels before starting a patient on PTU and to closely monitor these levels in the days and weeks following its initiation, to aid in both primary and secondary prevention.

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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