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Carbimazole-Induced Liver Injury: Review of Mechanisms, Clinical Presentation, and Therapeutic Management

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ABSTRACT

The incidence of carbimazole-induced liver injury (DILI) in patients treated for hyperthyroidism is infrequent, ranging from 0.1% to 0.5%. While the injury usually follows a cholestatic pattern, the condition can also present with mixed or cytolytic features, driven by either immune-mediated responses or the metabolic involvement of cytochrome P450 enzymes.We report the case of a 29-year-old woman with Graves' disease (free T4: 78 pmol/L) who developed severe hepatotoxicity two weeks after initiating 40 mg/day of Carbimazole. The patient presented with clinical jaundice and laboratory findings of significant cholestasis. After excluding viral, autoimmune, and structural etiologies, a diagnosis of carbimazole-induced hepatotoxicity was established.

Management included immediate cessation of the antithyroid drug, initiation of corticosteroid therapy (1 mg/kg/day), and a session of plasmapheresis to bridge the patient safely toward a thyroidectomy. Liver function showed marked improvement within one week of discontinuation. These findings suggest that when conventional cessation of the drug is insufficient to stabilize rapidly deteriorating liver enzymes, advanced extracorporeal therapies may serve as a crucial bridge to definitive surgical intervention. Ultimately, this report reinforces the necessity of vigilant monitoring of liver function tests during the initiation of carbimazole therapy. By advocating for proactive serial biochemical screening, we aim to standardize safer clinical practices and improve outcomes for patients requiring rapid definitive treatment in the setting of severe, unpredictable, and potentially life-threatening drug-induced liver injury caused by antithyroid medications.

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KEYWORDS:

Carbimazole, Drug-induced liver injury, Cytolytic hepatitis, Hyperthyroidism, Graves' disease

INTRODUCTION

Carbimazole, a thionamide antithyroid drug widely used in the management of hyperthyroidism, is rarely associated with drug-induced liver injury (DILI), with a reported incidence of 0.1–0.5%.[1] The hepatic injury pattern is predominantly cholestatic, though cytolytic and mixed forms have also been described. The underlying pathophysiology involves both metabolic activation through cytochrome P450 enzymes yielding hepatotoxic metabolites such as N-methylthiourea and immune-mediated mechanisms.

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[2] We present a case of carbimazole-induced cytolytic hepatitis and provide a comprehensive review of the diagnostic approach, pathophysiological pathways, and therapeutic strategies based on current evidence. Clinical diagnosis, immediate drug discontinuation, and transition to definitive therapy radioiodine or surgery remain the cornerstones of management. This report highlights the importance of systematic liver function monitoring in all patients initiated on carbimazole therapy.

CASE REPORT

We report the case of a 29-year-old woman presenting with severe hyperthyroidism due to Graves' disease (free T4: 78 pmol/L), treated with Carbimazole at a dose of 40 mg/day. Two weeks after treatment initiation, the patient presented with fatigue, anorexia, nausea, right upper quadrant discomfort, and progressive jaundice.

Physical examination revealed icteric sclerae and mild hepatomegaly without signs of chronic liver disease or decompensation. Laboratory results showed biological cholestasis associated with significant cytolysis: total bilirubin 368 mg/L, direct bilirubin 255.50 mg/L, indirect bilirubin 112.61 mg/L, ASAT: 99 IU/L, ALAT: 148 IU/L, GGT: 28 IU/L, PAL: 409 IU/L, TP: 100%, with sinusal tachycardia on ECG. Viral, autoimmune serologies, and abdominal ultrasonography were all negative, effectively ruling out competing etiologies, pointing toward drug-induced hepatotoxicity.

The antithyroid drugs (ATDs) were immediately discontinued, and the patient was started on corticosteroid therapy at 1 mg/kg/day, with a requirement for a plasmapheresis session before proceeding to radical treatment via surgery following the normalization of the thyroid function tests. We noted a marked improvement in liver function tests one week after stopping the ATDs.

MECHANISMS

The mechanisms underlying Carbimazole-induced hepatotoxicity are multifactorial and not yet fully elucidated. Two principal pathways have been proposed: direct metabolic hepatotoxicity and immune-mediated injury. [3] Carbimazole is a prodrug that is virtually completely converted to its active metabolite methimazole (MMI) following first-pass metabolism. [4] MMI is subsequently metabolized by the cytochrome P450 system, principally CYP2A6, yielding reactive toxic intermediates including N-methylthiourea and glyoxal.*(Li J)*

This metabolic pathway is dose-dependent, which explains the association between higher carbimazole doses and increased hepatotoxic risk. [4] An immuno-allergic mechanism has also been implicated, supported by the observation that hepatic injury occasionally occurs at low doses and does not always correlate with cumulative drug exposure. [3] Histopathological findings in affected patients typically reveal inflammatory infiltration with eosinophils, and intracanalicular cholestasis, features suggestive of a hypersensitivity reaction. [6] Cell-mediated immunity, involving T-lymphocyte activation against drug-protein adducts, may contribute to hepatocellular destruction in susceptible individuals.

Several factors have been identified that may predispose patients to carbimazole-induced liver injury, including female sex, advanced age, pre-existing liver disease, alcohol consumption, and genetic polymorphisms in CYP450 or UDP-glucuronosyltransferase enzymes. [3]

CLINICAL PRESENTATION

The onset of hepatotoxicity typically occurs within the first three months of therapy, with a reported mean onset of approximately 36 days following initiation. [6]

Patients with carbimazole-induced DILI may present with a spectrum ranging from asymptomatic transaminase elevation to fulminant hepatic failure. [2]

Symptomatic cases typically manifest with jaundice, pruritus, fatigue, nausea, anorexia, dark urine, and right upper quadrant pain. [7]

The diagnostic approach relies on the following key steps: Biochemical characterization: Liver function tests allow classification of the injury pattern. A hepatocellular pattern (R ratio ≥ 5) reflects cytolytic hepatitis with predominant ALT elevation; a cholestatic pattern (R ratio ≤ 2) presents with elevated alkaline phosphatase and bilirubin; and a mixed pattern falls between both. The R ratio is calculated as (ALT/ULN) ÷ (ALP/ULN). [8] Exclusion of competing etiologies: Viral hepatitis (HAV, HBV, HCV, HEV, EBV, CMV), autoimmune hepatitis, biliary obstruction, ischemic hepatitis, and thyrotoxicosis-related liver dysfunction must be systematically excluded through serology, imaging, and clinical correlation. [9]

Causality assessment: The RUCAM (Roussel-Uclaf Causality Assessment Method) scale provides a structured, validated framework for establishing a causal relationship between the suspected drug and the liver injury, taking into account the temporal relationship, course of the reaction, known risk factors, and exclusion of other causes. [9]

MANAGEMENT

Management of carbimazole-induced hepatotoxicity follows a stepwise, individualized therapeutic approach guided by the severity of liver injury and the clinical status of the thyrotoxic patient.

Step 1: Immediate drug discontinuation: Upon suspicion of DILI, carbimazole must be stopped immediately without dose tapering. Resolution of liver enzyme abnormalities generally occurs within three to eight weeks of drug withdrawal. [10]

Step 2: Management of hyperthyroidism: Discontinuation of carbimazole necessitates urgent reassessment of the therapeutic strategy for hyperthyroidism. The use of potassium iodide (Lugol's solution) can provide temporary thyroid hormone suppression and is particularly useful as a bridge to definitive therapy. Beta-blockers (propranolol or atenolol) should be maintained or initiated to control adrenergic symptoms and protect against thyroid storm. [1]

Step 3: Switching to propylthiouracil (PTU): Although cross-reactivity between thionamides is theoretically possible, the hepatic injury patterns of carbimazole and PTU differ fundamentally: carbimazole induces predominantly cholestatic injury, while PTU causes hepatocellular necrosis through distinct metabolic pathways.

[11] Switching to PTU as a short-term bridge to definitive therapy has been reported without recurrence of hepatotoxicity in selected cases [8], though this strategy remains controversial and should be approached with close liver function monitoring.

Step 4: Definitive therapy: International guidelines from the European Thyroid Association (ETA) and the American Thyroid Association (ATA) strongly recommend definitive therapy radioactive iodine (RAI) or thyroidectomy as the treatment of choice in the context of antithyroid drug-induced hepatotoxicity. [12] RAI is generally preferred in the absence of contraindications, particularly active ophthalmopathy or pregnancy.

Thyroidectomy is indicated in patients with large goiter, compressive symptoms, or those who are poor candidates for RAI. Euthyroidism should ideally be achieved before surgery to minimize perioperative risk. Step 5 :Supportive hepatological management: In cases of severe hepatotoxicity with coagulopathy, hyperbilirubinemia, or encephalopathy, hepatological consultation and intensive monitoring are mandatory. [15] N-acetylcysteine (NAC) has been explored as a hepatoprotective agent in drug-induced acute liver failure and may be considered in severe cases . [7] Referral to a liver transplant center should be arranged promptly in patients with signs of acute liver failure. [13]

FOLLOW-UP AND MONITORING

Routine baseline liver function testing is recommended prior to initiation of carbimazole therapy, and periodic monitoring should be performed every 4 to 6 weeks during the first three months given the peak incidence of hepatotoxicity during this window. [6]

Rechallenging with carbimazole is absolutely contraindicated following confirmed drug-induced hepatotoxicity. [1]

Thyroid function should be closely co-monitored, and the chosen definitive therapy RAI or surgery should be planned without delay to prevent recurrence of thyrotoxicosis and its own hepatic consequences. [15]

DISCUSSION

This case illustrates the diagnostic and therapeutic challenges of carbimazole-induced cytolytic hepatitis occurring in the context of active hyperthyroidism. The coexistence of thyrotoxicosis which independently causes mild liver enzyme elevations and drug-induced hepatocellular injury creates a clinically complex diagnostic scenario that demands a structured, systematic approach.

The distinction between the cholestatic injury pattern classically attributed to carbimazole and the cytolytic pattern observed in this case underscores the heterogeneity of thionamide-induced DILI, which may reflect individual differences in metabolic enzyme activity and immune susceptibility. [3] A recent systematic review of antithyroid drug-related liver injury reported that hepatocellular and mixed patterns, while less frequent than cholestatic forms, are associated with more severe outcomes and higher rates of liver-related mortality. [14]

The current evidence supports a Preventive care strategy with early definitive therapy, avoiding prolonged reliance on alternative antithyroid pharmacotherapy following hepatotoxic events. Multidisciplinary collaboration between endocrinologists and hepatologists remains essential in optimizing outcomes for this challenging patient population. [15]

CONCLUSION

Carbimazole-induced cytolytic hepatitis is a rare but clinically significant complication of antithyroid therapy that requires prompt recognition and immediate management. The pathophysiology involves both CYP450-mediated metabolic activation and immune-allergic mechanisms. Diagnosis relies on biochemical characterization, systematic exclusion of alternative etiologies, and causality scoring using RUCAM. The therapeutic cascade prioritizes immediate drug withdrawal, temporary thyrotoxicosis control, and rapid transition to definitive therapy with RAI or thyroidectomy. Routine liver function monitoring throughout carbimazole therapy and early multidisciplinary referral in severe cases remain the pillars of safe clinical practice.

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