

Propylthiouracil-Induced Toxic Hepatitis — Report of One Case

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Abstract

Although asymptomatic liver dysfunction is observed in up to one-third of patients who received propylthiouracil, severe hepatotoxicity is rarely seen. Here we report a case of a 47-year-old female with Graves' disease previously having normal liver function tests. After 5 weeks of propylthiouracil administration, she developed jaundice and anorexia. Liver function tests showed elevated aminotransferase and total bilirubin level. Propylthiouracil was discontinued immediately and liver function improved gradually. The patient was uneventful three months after the flare of hepatitis. The diagnosis of propylthiouracil-induced toxic hepatitis was established by the temporal relation between the drug initiation and hepatic dysfunction, and exclusion of other causes of liver damage including viral hepatitis, alcoholic liver disease, autoimmune hepatitis, hereditary disorders, and other hepatotoxins. (J Intern Med Taiwan 2008; 19: 266-269)

Key Words : Propylthiouracil, Toxic hepatitis, Graves' disease

Introduction

Propylthiouracil-induced toxic hepatitis is a rare complication of the drug¹⁻⁴. The clinical manifestations are usually nonspecific except abnormal liver function tests. Discontinuation of propylthiouracil is warranted if hepatic function deteriorated during the

use of the drug³. Here we report a mid-aged woman who developed propylthiouracil-induced toxic hepatitis.

Case Report

A 47-year-old female was diagnosed with Graves' disease in August 2006, with the initial pre-

sensation of palpitation and body weight loss. She visited endocrinology department in other hospital, where she was prescribed two weeks of propylthiouracil 150 mg and propranolol 30 mg daily in three divided doses. She continued the treatment in our hospital with propylthiouracil 300 mg and propranolol 30 mg daily in three divided doses for another three weeks, until the development of anorexia, yellowish skin and dark colored urine in late September 2006. She had received a general health examination a few months ago, and was informed a normal liver function test. She denied alcohol drinking or use of other drugs. She had history of thyroid enlargement 10 years ago with treatment of herbal medicine for short duration. Her mother also had history of hyperthyroidism with subtotal thyroidectomy.

She was found to have extremely elevated liver enzymes and jaundice on September 29, 2006. ALT was 1052 U/L, AST was 772.5 U/L and total bilirubin was 9.4 mg/dL with direct form of 6.0 mg/dL. So she was admitted. On physical examination, the patient was alert. Skin color and sclera were deeply icteric. Blood pressure was 120/80 mmHg and pulse rate was 80 beats per minute. Bilateral lobes of thyroid gland were enlarged. Abdomen was soft without tenderness, and the liver and spleen were not palpable. Neither ascites nor edema was detected.

On admission, ALT and AST were 1168 U/L and 898 U/L, respectively. Alkaline phosphatase was 271 U/L. Serum albumin was 3.6 g/dL. Total bilirubin was 9.2 mg/dL with direct form of 5.9 mg/dL. Prothrombin time was 10.4 sec with INR 0.89, and activated partial thromboplastin time was 27.0 sec. Thyroid function showed TSH < 0.03 μ U/mL, T3 158 ng/dL and T4 8.10 μ g/dL. Anti-TSH antibodies were elevated, but anti-microsomal antibodies were negative. Anti-smooth muscle antibodies, anti-mitochondrial antibodies, antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA) were all negative. Hepatitis B surface antigen, hepatitis B core antibodies, hepatitis C antibodies were

negative. Viral markers of hepatitis A, cytomegalovirus and Epstein-Barr virus were also negative. Ultrasonography of abdomen revealed neither cirrhotic change nor focal lesions.

She was diagnosed to have acute toxic hepatitis induced by propylthiouracil. Propylthiouracil was discontinued immediately. Propranolol was continued to control hyperthyroid symptoms. The liver function test improved gradually. She was discharged 7 days later, with ALT 236.7 U/L, AST 101.8 U/L and total serum bilirubin 3.9 mg/dL. In OPD follow-up, the liver function tests returned to normal limits on October 31, 2006. Then she was referred to general surgical department and had subtotal thyroidectomy done on November 1, 2006. The pathology of thyroid tissue reported nodular hyperplasia with cystic degeneration of the right lobe of thyroid, and nodular hyperplasia of the left lobe. She was followed in surgical department and mild hypothyroidism was found.

Discussion

Hepatotoxicity is one of the most widely reported adverse effects of propylthiouracil. Although up to one third of patients who received propylthiouracil develop asymptomatic liver function abnormalities, severe liver toxicity is rare, with the incidence of approximate 1%^{1-2,5}. It may occur at all ages but more common in younger patients⁴. A female predominance was observed probably due to a higher incidence of Graves' disease in female population^{3,4}. The onset of hepatotoxicity varied from just one day to 14 months, but usually within first few months after the beginning of propylthiouracil^{2,4,6}. The hepatotoxicity was not associated with liver function before propylthiouracil administration, dosage of propylthiouracil and duration of its use^{2,4}.

The pathophysiology of propylthiouracil-induced hepatotoxicity is still unclear. Some evidence implied that autoimmune disorder may play an important role^{3,7,8}. It is believed that the use of propy-

lthiouracil may cause ANCA-positive vasculitis¹. In one case report of hepatitis after propylthiouracil administration, positive ANA and slightly positive anti-smooth muscle antibodies had been found too⁷. The clinical presentation of propylthiouracil-induced hepatotoxicity includes jaundice, right upper quadrant abdominal pain, nausea, vomiting, malaise and abnormal liver function tests. The definite diagnosis depends on the result of liver biopsy, which varies from hepatocellular inflammation to submassive or massive hepatic necrosis, with or without cholestasis. SPECT imaging with Tc-99m may be considered as a less invasive procedure⁹. Drug rechallenge is not recommended to avoid recurrence of hepatic injury³. Lymphocyte stimulating test may be performed but with limited sensitivity³. The practical diagnostic criteria usually include evidence of liver dysfunction temporally related to drug initiation and exclusion of other causes of liver damage such as viral hepatitis, alcoholic liver disease, autoimmune hepatitis, hereditary disorders, or other hepatotoxins^{1,7}.

Propylthiouracil should be discontinued promptly once hepatotoxicity was detected³. The liver function tests normalized in most patients between 16 to 145 days after discontinuation of propylthiouracil². Prolonged elevation of liver enzymes despite clinical improvement is possible⁶. Steroids are another common treatment option, which have anti-thyroid and anti-inflammatory function⁴. Liver transplantation is reserved for severe hepatic failure, and there have been successful cases in review³. Because hyperthyroidism itself may cause elevations of liver enzymes, immediate radioactive iodine therapy followed by oral iodide is suggested in some studies^{3,8}. In our case, radioactive iodine was not given because T3 and T4 level were within normal limits and propranolol was working well to control symptoms. Amiodarone has been reported to successfully control hyperthyroidism too¹⁰. Whether methimazole or carbimazole can be used instead under the circumstance is controversial^{1,3}. Methimazole and carbima-

zole typically cause cholestatic hepatitis while propylthiouracil causes cytotoxic hepatitis^{3,8}.

In our reported case, the significant abnormalities of liver function tests was noted in five weeks of propylthiouracil use, and we had ruled out other possible reasons of hepatic damage by serology and a thorough history. The patient recovered in about one month after discontinuation of the drug. Although histological evidence was lacking, we still felt confidently to make this diagnosis by applying the practical criteria mentioned above. In conclusion, toxic hepatitis is a rare complication of propylthiouracil. Although mild liver enzyme elevation was found in a large proportion of patients using propylthiouracil, these patients can continue to use the drug with caution if they were anicteric and asymptomatic⁴⁻⁵. Prompt discontinuation of propylthiouracil is required if significant liver function abnormalities, jaundice or symptoms like malaise and anorexia occurred.

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Propylthiouracil 引起的毒物性肝炎—— 病例報告及文獻回顧

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摘 要

使用propylthiouracil的病人當中，高達三分之一的病人會發生無症狀的肝功能失調，嚴重的肝毒性卻是非常罕見。我們在此報告一個病例：一位四十七歲患有葛瑞夫茲症的女性，之前肝功能檢查為正常，在服用五週的propylthiouracil之後，發生黃疸和食慾下降的現象。肝功能檢查顯示轉胺酶和總膽紅素數值升高。病患立即停用propylthiouracil並且肝功能逐漸恢復。經追蹤這名個案在肝炎發生三個月後仍平安無事。Propylthiouracil引發的肝毒性的診斷是藉由藥物開始使用與肝功能失調呈暫時性相關，並排除其他造成肝損傷的原因：例如病毒性肝炎、酒精性肝病、自體免疫性肝炎、遺傳疾患，以及其他肝毒性物質等。