PROPYLTHIOURACIL-ASSOCIATED HEPATITIS

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The case of a 43-year-old female with propylthiouracil-induced hepatitis is reported. The case is unique because the patient's liver function deteriorated 2 weeks after medication was discontinued.

Key words • hepatitis • propylthiouracil • Graves' disease

There are several reports[1-10] of propylthiouracil-associated hepatitis in the literature. The outcome was fatal in four cases.[6-10] The exact mechanism of propylthiouracil hepatotoxicity is unknown, and there are no parameters to determine which patients are susceptible to this toxic effect. This case is reported because of a persistent deterioration in liver function for 2 weeks, despite discontinuation of propylthiouracil. This course has not been described in the reports of patients surviving propylthiouracil-induced hepatitis.

CASE REPORT

A 43-year-old woman was admitted to the hospital with nausea, anorexia, pruritus, dark-colored urine for 2 weeks, and yellow discoloration of her eyes for 1 week. Three months before the onset of these symptoms she was diagnosed as having Graves' disease, with hyperthyroidism, and was started on propylthiouracil 600 mg a day and propranolol 60 mg a day. At the time of admission, she was maintained on only propylthiouracil 300 mg a day. The patient denied any history of chronic liver disease, blood transfusions, alcohol intake, or drug abuse. She had no contact with any person with hepatitis. On physical examination, there was marked icterus, normal vital signs, diffuse thyromegaly of twice normal size, and epigastric tenderness. There was no hepatomegaly, splenomegaly, or lymphadenopathy. The remainder of the physical examination was within normal limits.

Laboratory values at the time of admission included a total bilirubin 6.4 mg/dL (0.2 to 1.2), alkaline phosphatase 292 IU/L (30 to 115), serum glutamic oxaloacetic transaminase 926 IU/L (7.0 to 40.0), and prothrombin time 14.1 seconds (control 11 seconds). A complete blood cell count, including differential cell count, was normal. Propylthiouracil was discontinued. However, the patient's liver function continued to deteriorate (Table).

The patient was started on a "hepatic aid" nutritional supplement and lactulose. Abdominal sonogram and computerized tomography scan showed no evidence of gallbladder disease or malignancy. Hepatitis profile for type A and type B was negative. Cytomegalovirus and Epstein-Barr virus titers showed no evidence of infection. Antinuclear antibody test was positive with a titer of 1:40.

On the 12th day after discontinuation of pro-

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TABLE. LIVER FUNCTION STUDIES

Days After Discontinuation of PTU	Bilirubin (mg/dL) Total	SGOT AST (IU/L)	ALT (IU/L)	Prothrombin (pt secs)	Alkaline Phosphate (IU/L)
1	6.4	926		14.1	292
4	13.3	1306		14.7	
6	18.8	1655	1120	17.8	300
9	24.3	1693	1139		281
10	25.7	1560			294
11	23.7	1389	936		261
13	24.5	977		14.1	273
16	20.7	539			249
23	9.8	205			197
30	5.0	185		13.2	163

pylthiouracil, liver function studies began to show improvement. Liver function gradually improved and the patient was discharged from the hospital 5 weeks after admission. She received radioactive iodine therapy for Graves' disease prior to discharge and was maintained on propranolol 60 mg/day.

Ten weeks after propylthiouracil cessation, she had a lymphocyte sensitization test at Brooklyn's University Hospital Immunology Laboratory. There was no evidence of propylthiouracil sensitization. The patient is now euthyroid, with normal liver function studies and a negative antinuclear antibody test.

DISCUSSION

Hanson[7] proposed the following practical criteria for diagnosing drug-induced hepatitis:

1. Clinical and laboratory evidence of hepatocellular dysfunction.
2. Onset of symptoms temporally related to drug therapy.
3. No serologic evidence for current hepatitis A or B cytomegalovirus infections or Epstein-Barr virus.
4. Absence of an acute hepatic insult (shock, sepsis).
5. No evidence of chronic liver disease.
6. Absence of other concomitantly administered drugs, especially known hepatotoxins.

This patient satisfies the criteria for propylthiouracil hepatitis. Propranolol has not been implicated as a hepatotoxin. Furthermore, our patient was maintained on propranolol while awaiting the full therapeutic effect of radioactive I 131 treatment. There was no deterioration of liver function during this period.

The mechanisms proposed for propylthiouracil hepatotoxicity are (1) a direct cytotoxic effect and (2) host idiosyncrasy.[7] The possibility of an autoimmune cause of this type of hepatotoxicity has not been considered in the literature. In cases of propylthiouracil-induced hepatitis in which a liver biopsy was obtained, all showed a histologic picture compatible with chronic active hepatitis. Several reports strongly suggest the autoimmune nature of hepatitis B negative chronic active hepatitis.[11,12]

A suppressor T cell defect has been demonstrated in patients with Graves' disease.[13] This defect has been postulated as the basis of autoimmune thyroid disease.[14] Propylthiouracil, or its metabolites, may induce an autoimmune reaction to the liver in susceptible patients. There are three progressive stages in the development of autoimmune diseases: autorecognition, autoimmune state, and overt autoimmune disease. This phenomenon can be triggered by any stress—physical, mental, or infectious.

Removal of the stress, even at the second stage (autoimmune state), results in arrest of the process and return to normal physical state. Thus, in the majority of cases, timely cessation of propylthiouracil results in recovery of normal liver function.[15] Patients with a fatal outcome may have progressed to complete autoimmune disease state before discontinuation of propylthiouracil therapy.

This patient may have been close to the complete autoimmune disease state, which may explain the continued deterioration of liver function despite propylthiouracil cessation. The negative T-cell sensitization test could be due to the extended period (6 or more weeks) from cessation of propylthiouracil to the time of testing. A trial of immunosuppresive therapy may be appropriate in patients with propylthiouracil-associated hepatitis who fail to improve with drug cessation.

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