Alerts, Notices, and Case Reports

Propylthiouracil-Induced Hepatotoxicity

JAMES T. HARDEE, MD
ANGELA L. BARNETT, MD
ABDUL THANNOUN, MD
BIJAN EGHTESAD, MD
DONALD WHEELER, MD
M. MAZEN JAMAL, MD
Albuquerque, New Mexico

PROPYLTHIOURACIL (PTU) is a thioamide derivative widely used in the treatment of hyperthyroid conditions. Despite its relatively safe profile, hepatotoxicity remains a serious, albeit rare, complication. Having been reported in nearly 30 cases in the English-language literature since its introduction in 1947,[1-26] PTU-induced toxic liver injury must be considered in any patient receiving this drug in whom symptoms of hepatic dysfunction appear. Patients may present with jaundice, right upper quadrant abdominal pain, malaise, nausea, vomiting, and anorexia. Reported sequelae of PTU hepatotoxicity range from rapid recovery following discontinuation of the drug* to fulminant hepatic failure and death.[2,3,12,13,18] A recent review of drug hepatotoxicity lists PTU-induced hepatitis as an "idiosyncratic" reaction with immunologic mechanisms, hypersensitivity, and direct toxicity among the postulated pathogeneses.[27]

A patient was recently transferred to our institution whose condition fit the description of PTU-induced hepatic failure. We report the case and describe the histopathologic findings on liver biopsy.

Report of a Case

The patient, a 37-year-old woman, was diagnosed with Graves' disease five months before her presentation, and a regimen of oral propylthiouracil, 200 mg per day, was started. At that time, baseline laboratory values were as follows: alkaline phosphatase, 298 IU per liter (normal, 130 to 150); total bilirubin, 17.1 μmol per liter (1.0 mg per dl [normal, 2 to 18 μmol per liter]); direct bilirubin, 3.4 μmol per liter (0.2 mg per dl [normal, 0 to 4 μmol per liter]); and aspartate aminotransferase (AST), 20 IU per liter (normal, 14 to 34). Two months later, the dose of PTU was increased to 400 mg daily for persistently elevated serum thyroid hormone levels. The patient tolerated this dosage for nearly three months until she contacted her primary physician because of weakness, fever, chills, nausea, vomiting, and a sharp right upper quadrant abdominal pain for several days. Also, her children had remarked about her "yellowish" appearance.

Propylthiouracil was discontinued at that time, and she was observed on an outpatient basis. Three days later, she was admitted to a community hospital for worsening malaise, jaundice, and nausea. Laboratory values on admission were as follows: thyroxine, 178 nmol per liter (13.8 μg per dl [normal, 51 to 142 nmol per liter]); AST, 1,490 IU per liter; alanine aminotransferase (ALT), 1,135 IU per liter (normal, 9 to 52); alkaline phosphatase, 486 IU per liter; total bilirubin, 284 μmol per liter (16.6 mg per dl); direct bilirubin, 169 μmol per liter (9.9 mg per dl); and prothrombin time, 15.5 seconds (control, 9.4 to 13.3 seconds). Tests for hepatitis A antibody immunoglobulin (Ig) M, hepatitis B surface antigen, and hepatitis B core antibody were all negative. A right upper quadrant abdominal ultrasonogram showed no sign of biliary dilation, and the liver, pancreas, and kidneys all appeared normal. By the second hospital day, her prothrombin time had increased to 17.2 seconds, and she was showing no signs of clinical improvement; she was thus transferred to our institution for evaluation.

On arrival at the University of New Mexico Health Sciences Center, Albuquerque, the patient was alert, deeply jaundiced, and continuing to have sharp, achy, right-sided abdominal pain. On questioning, she reported no recent travel history and no acetaminophen, alcohol, or injection drug use. She had no history of hepatitis exposure, blood transfusion, or other ingestions.

Her medical history was notable only for two vaginal deliveries, a postpartum tubal ligation, and a six-month history of hyperthyroidism. The patient was taking no medications as PTU had been discontinued five days before her transfer.

On physical examination, the patient was afebrile with a blood pressure of 134/73 mm of mercury, a pulse rate of 95 beats per minute, and a respiratory rate of 16 per minute. Chest auscultation revealed clear breath sounds bilaterally and a regular cardiac rate and rhythm without murmur. Her skin was jaundiced, and her sclerae were icteric; exophthalmos and lid lag were apparent. There were no stigmata of chronic liver disease. Her neck was supple, and the thyroid gland was three times normal size, smooth, firm, and nontender, with a prominent isthmus. Her abdomen was soft with moderate tenderness to palpation in the right upper quadrant. No guarding or rebound tenderness was noted, and no hepatosplenomegaly was appreciable. There was no asterixis or tremor, and deep tendon reflexes were normal.

Tests for hepatitis A antibody IgM, hepatitis B surface antigen, and hepatitis B core antibody were repeated and confirmed to be negative, as was a test for hepatitis C RNA by polymerase chain reaction. An erythrocyte sedi-

*References 1, 4–11, 15, 16, 19, 22, 23, 25, and 26.

(Hardee JT, Barnett AL, Thannoun A, Eghtesad B, Wheeler D, Jamal M: Propylthiouracil-induced hepatotoxicity. West J Med 1996; 165: 144–147)

From the Department of Internal Medicine, Division of Gastroenterology (Drs Hardee, Barnett, Thannoun, and Jamal); the Department of Surgery, Division of Liver Transplantation (Dr Eghtesad); and the Department of Pathology (Dr Wheeler), University of New Mexico School of Medicine, Albuquerque.

Reprint requests to James T. Hardee, MD, Department of Internal Medicine, University of New Mexico Health Sciences Center, 2211 Lomas Blvd NE, Albuquerque, NM 87106.

ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
ANA = antinuclear antibody
AST = aspartate aminotransferase
CMV= cytomegalovirus
EBV = Epstein-Barr virus
Ig = immunoglobulin
PTU = propylthiouracil

mentation rate was normal at 7 mm per hour, an antinuclear antibody (ANA) titer was 1:320, and an anti–smooth muscle antibody titer was 1:40. Tests for antimitochondrial antibody, antimicrosomal antibody, anticentromere antibody, and antihistone antibody IgG were all negative. An Epstein-Barr virus (EBV) IgG test was positive at 1:640, indicating previous exposure to EBV, and a CMV IgG level was within normal limits at 81.3 Antibody Units per ml. Cultures of blood and urine were negative for growth.

The patient underwent a transjugular liver biopsy on hospital day 1, which subsequently revealed severe acute hepatitis with portal-to-central-bridging necrosis (Figure 1). A transjugular approach was chosen to minimize bleeding complications because her prothrombin time had climbed to 21.4 seconds. Her condition continued to deteriorate on hospital day 2, as shown by the following laboratory values: ALT, 1,449 IU per liter; AST, 2,052 IU per liter; alkaline phosphatase, 485 IU per liter; total bilirubin, 369 μmol per liter (21.6 mg per dl); direct bilirubin, 299 μmol per liter (17.5 mg per dl); and prothrombin time, 21.9 seconds. During this time, she had episodes of hypoglycemia, tachycardia, and mental status changes and was transferred to the medical intensive care unit for closer monitoring. Radioactive iodine ablation of the thyroid was not attempted because of the iodine-containing contrast medium given the patient during fluoroscopic transjugular biopsy. A regimen of intravenous methylprednisolone sodium succinate (80-mg load, followed by 60 mg every 8 hours), lithium carbonate, and propranolol hydrochloride was started for the control of thyrotoxicosis. Within 48 hours, an improvement was noted in the following laboratory values: ALT, 894 IU per liter; alkaline phosphatase, 369 IU per liter; total bilirubin, 315 μmol per liter (18.4 mg per dl); direct bilirubin, 299 μmol per liter (14.5 mg per dl); and prothrombin time, 28.4 seconds. She was then transferred out of the intensive care unit on a tapering course of oral prednisone with continued clinical and laboratory improvement. By hospital day 6, laboratory values were as follows: ALT, 456 IU per liter; AST, 187 IU per liter; alkaline phosphatase, 290 IU per liter; total bilirubin, 255 μmol per liter (14.9 mg per dl); direct bilirubin, 197 μmol per liter (11.5 mg per dl); and prothrombin time, 19.6 seconds.

The patient was discharged to home on hospital day 11 on a regimen of lithium carbonate and a tapering course of oral methylprednisolone and was scheduled for definitive thyroid treatment.

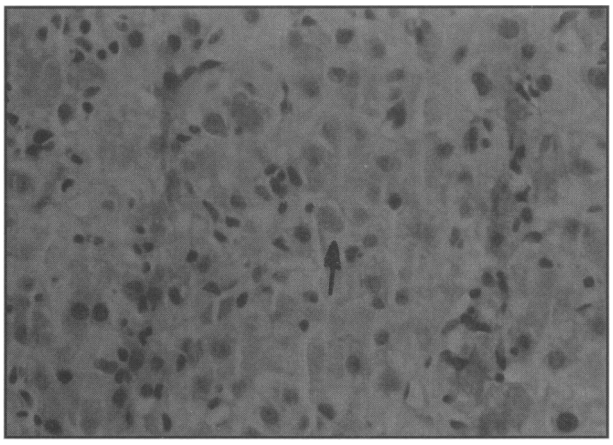

Figure 1.—A transjugular liver biopsy is shown (original magnification × 400). Prominent mononuclear cell infiltrate is present throughout the lobules. Numerous acidophil bodies are identified **(arrow)**.

Discussion

Although propylthiouracil has been used safely for many years in the treatment of hyperthyroid conditions, several adverse reactions have been reported, including agranulocytosis,[28] leukopenia,[29,30] hemolytic anemia,[31] aplastic anemia,[32] disseminated intravascular coagulation,[33] cutaneous vasculitis,[34,35] and interstitial pneumonitis.[36]

Hepatotoxicity from PTU has been one of the most widely described adverse reactions. A cohort study in 1993 revealed that ALT values became elevated in 33% (15 of 45) of patients studied after two months of PTU administration.[24] These elevations were transient, abating with the reduction in medication dose over time, and the patients were asymptomatic. The temporal relationship between ALT elevation and the start of PTU treatment suggests that the elevation was indeed induced by PTU use, thus reflecting subclinical acute hepatocellular injury evidenced by aminotransferase leakage. The conclusion was that these findings contradict previous observations that PTU-induced hepatitis is rare and usually severe.

Drug-induced hepatocellular injury is a difficult diagnosis to establish and is often one of exclusion. Etiologic agents that must be investigated include hereditary disorders, viral infections (including hepatitis A, B, C, CMV, and EBV), and other hepatotoxins. It has also generally been accepted that hyperthyroidism itself can cause abnormalities in liver function test values. In one series, liver biopsy specimens of patients with thyrotoxicosis were examined, and Graves' disease was found to be associated with minimal hepatic changes and mild elevations of liver enzyme levels.[37] Ideal and practical criteria were proposed in 1984 to assist in the diagnosis of drug-induced hepatitis. Ideal criteria would include the histologic confirmation of hepatocellular injury and drug rechallenge, but this is seldom ethically possible. Practical criteria should include clinical and laboratory evidence of hepatocellular dysfunction; the onset of symptoms temporally related to the start of drug therapy;

no serologic evidence for current infection with hepatitis A, B, or C, CMV, or EBV; the absence of an acute hepatic insult such as shock or sepsis; no evidence of chronic liver disease; and the absence of other concomitantly administered drugs, especially known hepatotoxins.[13]

In the past, it has been difficult to ascribe characteristic histologic features to PTU-induced hepatitis due to the small number of biopsies actually done. Of the ten documented cases of PTU-induced hepatitis in which liver biopsies were taken, histopathologic features have ranged from mild portal inflammation to submassive or massive hepatic necrosis with bridging fibrosis.[2-6,10,12,18,19,26]

In 1976 the case of a 24-year-old woman with PTU hepatitis who underwent liver biopsy three weeks after her initial presentation was described. The biopsy showed hepatocellular necrosis with lobular disarray, free acidophil bodies, ballooning degeneration, and bridging necrosis.[6] A postmortem examination of liver disease performed on a 20-year-old woman with PTU hepatitis in 1982 revealed hepatic nodules and fatty degeneration consistent with fibrosis following submassive hepatic necrosis.[12] A 56-year-old man with PTU hepatitis had acute and chronic inflammatory cells on percutaneous liver biopsy performed two days after his presentation. Under electron microscopy, the specimen revealed autophagic vacuoles, residual bodies, both contracted and swollen mitochondria, and dilated, smooth endoplasmic reticulum.[5]

Microscopic examination of the transjugular liver biopsy specimen in our patient revealed a prominent mononuclear infiltrate throughout the lobules, and numerous acidophil bodies were identified in a background of pronounced hepatocellular dropout (see Figure 1). There was occasional interstitial hemorrhage in the central regions, and the portal tracts contained a pronounced mononuclear cell infiltrate, predominantly lymphocytes. An iron stain was negative, and there was no evidence of hyaline globules, viral inclusions, granulomas, or neoplasia. The histologic features were consistent with severe acute hepatitis with portal-to-central-bridging necrosis.

Although a regimen of intravenous steroids was initiated to control the patient's thyrotoxic state, a rapid improvement in aminotransferase and bilirubin levels and prothrombin time was incidentally noted. Whether this improvement was due in part to the steroid therapy or simply to the discontinuation of PTU seven days earlier is unclear. A search of the literature found no record of controlled or uncontrolled trials of corticosteroid treatment of drug-induced hepatitis, and the efficacy of this therapy can only be described as anecdotal at this time.

This case has been attributed to PTU toxicity because it fulfills Hanson's criteria.[13] Before treatment with PTU, our patient had no clinical or biochemical evidence of hepatic dysfunction. The marked rise in aminotransferase levels and the close temporal relationship of these changes to the start of PTU therapy again supports this diagnosis. It should be noted that given the positive ANA test (1:320) and the slightly positive anti–smooth muscle antibody test (1:40), the possibility of autoimmune hepatitis cannot be completely ruled out. Antinuclear antibody titers can be elevated in many conditions involving hepatocellular damage, and the obvious temporal relationship to PTU therapy makes this the most likely cause.[38]

Because an early recognition of PTU-induced hepatic failure and prompt withdrawal of the drug may prevent progression from mild to severe disease, it may be prudent to discuss signs and symptoms of liver disease and other side effects with patients. Jaundice, pruritus, dark urine, abdominal pain, anorexia, or malaise should signal a patient to seek medical attention.

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Venlafaxine Hydrochloride and Chronic Pain

KIRK TAYLOR, MD
MICHAEL C. ROWBOTHAM, MD
San Francisco, California

CLINICAL TRIALS of tricyclic antidepressants have shown efficacy for both chronic headaches and neuropathic pain.[1] The tricyclic antidepressants useful for chronic pain block the neuronal reuptake of both serotonin and norepinephrine. Serotonin-selective reuptake-inhibitor antidepressants have shown little or no efficacy when compared with placebo or tricyclic antidepressant use for neuropathic pain.[2] Unfortunately, the use of these drugs for chronic pain is limited by numerous side effects such as sedation, cognitive impairment, orthostatic hypotension, cardiac conduction abnormalities, dry mouth, and constipation. Many of these effects are due to the affinity of tricyclic antidepressants for the muscarinic-cholinergic, histaminic, and α_1-adrenergic receptors. Venlafaxine hydrochloride is a new antidepressant medication that, like the tricyclic antidepressants, inhibits the neuronal reuptake of both serotonin and norepinephrine.[3] Venlafaxine does not bind to muscarinic-cholinergic, histaminic, and α_1-adrenergic receptor sites, making its side effect profile substantially different from and theoretically more benign than that of the tricyclic antidepressants.

We report our initial open-label experience with venlafaxine in treating patients with chronic pain, primarily headache and neuropathic pain. Pain relief was rated by combining a patient's rating of efficacy with the clinician's global impression after a minimum of four weeks of therapy. If a patient completed less than four weeks of treatment, efficacy was rated at the end of treatment. An 80% or greater reduction in pain severity was interpreted as complete pain relief, a 50% to 79% reduction as moderate pain relief, 20% to 49% as mild pain relief, and less than 20% reduction in pain as no pain relief.

Summary of Cases

Table 1 summarizes the cases of the first 12 patients we treated with venlafaxine. All of them had had inadequate pain relief or intolerable side effects with the use of at least one antidepressant. These patients completed at least two weeks of therapy with venlafaxine. One case was not included in the results because the patient had severe nausea after taking only two doses. Otherwise, the data were collected over a seven-month period after patients were examined for chronic pain or headache.

The eight women and four men had an average age of 54 years and an average pain duration of 7.7 years. Four patients had headache, seven had neuropathic pain, and one had atypical facial pain. Patients had tried an average of 2.6 different antidepressants before taking venlafaxine. Patients 6 and 10 were on concurrent opioid therapy with transdermal fentanyl citrate patches. Patients 5 and 9 did not complete four weeks of therapy. Patient 5 had complete relief of chronic daily headache for two weeks, but when pain began to return, she elected to discontinue venlafaxine instead of adjusting the dose. Patient 9 was taking several medications—mexiletine hydrochloride, carbamazepine, and valproate sodium—for pain due to a posterior fossa arteriovenous malformation after a stroke. With the start of venlafaxine therapy, an increased blood pressure required the cessation of fludrocortisone acetate used for the control of orthostatic hypotension. The patient experienced persistent drowsiness and unsteady gait after three weeks of therapy, and venlafaxine was discontinued. In the other ten patients, pain relief was rated as moderate in seven and mild in three at total daily dosages from 18.75 to 250 mg per day (average, 99 mg per day). The most common side effect was nausea, which was made manageable by starting therapy at 18.75 mg per day. Patient 10 had moderate relief of peripheral neuropathic pain at a dose of 37.5 mg per day but later reduced the dose to 18.75 mg per day because of subjective hyperthermia and impotence, with only a slight diminution of pain relief. Patient 12 later required a dose reduction from 75 mg twice a day to 37.5 mg twice a day because of worsened hypertension. She became normotensive without a loss of pain control. Based on these results, ven-

(Taylor K, Rowbotham MC: Venlafaxine hydrochloride and chronic pain. West J Med 1996; 165:147–148)

From the Pain Management Center, the Departments of Neurology and Anesthesia, University of California, San Francisco (UCSF), School of Medicine

This work was supported in part by National Institutes of Health Pain Research Training Grant NS07265.

Reprint requests to Michael C. Rowbotham, MD, UCSF Pain Management Center, 2233 Post St, Ste 104, San Francisco, CA 94115.